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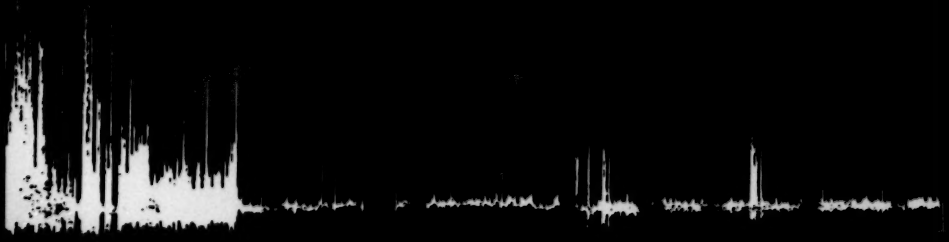

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RHEUMATIC HEART DISEASE IN SCARLET-FEVER PATIENTS TREATED WITH PENICILLIN*

A Follow-up Study after Seven Years

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BOSTON

IN 1948 Massell, Dow and Jones[1] reported that the administration of penicillin to rheumatic subjects with established streptococcal infections prevented the recurrence of rheumatic fever. Two years later, Denny and his co-workers[2] recorded a marked reduction in the frequency of this disease after penicillin therapy of streptococcal pharyngitis in normal adults. In this study, and in a subsequent one carried out by Wannamaker et al.,[3] 978 men with this type of sore throat were given penicillin whereas 996 control patients, selected only on the basis of the Air Force serial numbers, received no specific treatment. On the basis of the diagnostic criteria of Jones[4] it was found that 2 of the subjects given the antibiotic and 28 of those not treated exhibited definite rheumatic fever; there were 3 cases of possible rheumatic fever among the treated and 7 in the control group. Thus, the rheumatic state occurred seven times more often in treated than in untreated patients. In a study of the effect of chlortetracycline (Aureomycin) on streptococcal infection Houser and his colleagues[5] claimed a fourfold reduction in rheumatic fever in subjects receiving this drug as compared with untreated controls.

In 1950 Weinstein, Bachrach and Boyer,[6] using less rigid diagnostic criteria than those proposed by Jones, suggested that the penicillin therapy of scarlet fever might not reduce appreciably the frequency of rheumatic fever. Rheumatic carditis was reported to have occurred in 7 per cent of 167 patients on the basis, in all but 1, of abnormal electrocardiographic patterns that appeared after a latent period. No untreated controls were included in this study because it was considered unwise to risk the development of suppurative complications, which tend to be quite common and are often severe in children; this was deemed especially important since it was established that penicillin therapy was highly effective in completely eliminating such sequelae.

Because of the discrepancies in results that had been reported and to determine the validity of the diagnostic criteria employed by us in 1946, it was decided in 1953 to restudy the patients who had been treated seven years earlier, primarily from the standpoint of their cardiac status. It is the purpose of this paper to report the findings in 110 subjects who were examined seven years after they had been treated for scarlet fever with pencillin, and to point out that an appreciable number of those who had been suspected of having acute rheumatic fever when first seen now have positive evidence of rheumatic heart disease, whereas none of those in whom this disease had not been considered to be present now exhibit any cardiac abnormalities. The data obtained tend to validate the abnormal electrocardiogram in a patient with proved streptococcal pharyngitis as an important criterion for the diagnosis of rheumatic fever.

METHODS

An attempt was made to get in touch with all the patients who had been studied seven years earlier. Because some of them could not be located and others did not reply to the requests to return, only 110 were available for the present investigation.

Each of the patients was seen by at least two and often three examiners. To eliminate bias as much as possible the interviews and other studies were carried out without any information concerning the clinical situation in 1946 except in a few cases, in which the examinations were performed by the other two investigators before being done by the one who knew the previous status. The cardiologist (N.H.B.) was not informed, in any case, of the diagnosis made seven years previously. The subjects in whom probable or positive evidence of rheumatic heart disease was

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thought to have been present in 1953 were brought back for re-examination two or three months later; the records of the findings of the previous visit were not made available to the cardiologist before his re-examination of the patient.

In each case a carefully detailed history was obtained concerning episodes of any type of pharyngitis, proved attacks of streptococcal sore throat or illnesses suggestive of rheumatic fever that had occurred between 1946 and 1953. This information, in many cases, was obtained not only from the patients but also from their parents.

Physical examinations were carried out in all 110 cases. The heart was studied at rest and after exercise and in the recumbent, sitting and standing positions. All the patients were subjected to fluoroscopy, and a careful note was made of the shape of the cardiac silhouette and the size of the various chambers. In those in whom the presence of rheumatic heart disease was suspected, an electrocardiogram was taken, fluoroscopy was repeated with a barium swallow to detect enlargement of the left atrium and 6-foot roentgenograms of the chest were made in the posteroanterior and right anterior oblique positions. In the subjects with normal cardiac findings by physical examination, x-ray study of the chest was omitted.

TABLE 1. *Data in Patients with Scarlet Fever Treated with Penicillin (1946).*

No. of Cases	Patients 2-15 Yr. of Age	Patients Under 10 Yr. of Age	Isolation of Group A *Str. Pyogenes*	Occurrence of Sore Throat for 24 Hr. or Less before Therapy	Occurrence of Sore Throat for 48 Hr. or Less before Therapy	Penicillin Treatment
			%	%	%	
167	150	126	100	57.6	71.7	15,000 units intramuscularly every 3 hr. for 10 days

RESULTS

Summary of Observations Made in 1946-47

To provide a basis for the proper evaluation of the observations made in 1953, the results of the studies carried out in 1946[6] are briefly summarized here.

One hundred and sixty-seven cases of scarlet fever were treated by intramuscular injection of 15,000 units of penicillin every three hours for ten days. Group A *Streptococcus pyogenes* was isolated in every case at the time of entry to the hospital. Symptoms of pharyngitis had been present for only twenty-four hours in 57.6 per cent and for forty-eight hours or less in 71.7 per cent of the patients at the time antibiotic therapy was started (Table 1). One hundred and fifty of the patients were two to fifteen years of age, and 126 were under ten years. Physical examinations were carried out daily, cultures of the respiratory tract were made a minimum of every other day, and blood was drawn for serologic studies once a week. The urine was examined three times a week. Electrocardiograms were obtained daily in most cases and every other day in a few. All the patients remained in the hospital for a minimum of three weeks; some stayed for longer periods.

In 12 of the 167 patients acute rheumatic fever was thought to have developed despite the use of penicillin. The average latent period between the onset of the streptococcal sore throat and the appearance of manifestations suggestive of rheumatic fever was nine and two-tenths days (Table 2). Five patients had elevations of temperature during the period when rheumatic activity was presumed to be present; in 7, there was no fever during this time. In 1 child an apical systolic and an aortic diastolic murmur developed, without any electrocardiographic abnormalities or joint disturbances; another had migrating polyarthritis, cardiomegaly, a transient mitral diastolic and persistent apical systolic murmur and prolongation of both PR and QT_c intervals that appeared after a latent period. In both of these cases Jones's criteria for the diagnosis of rheumatic fever were fulfilled. Ten other patients had prolonged atrioventricular conduction time; in each case the PR and QT_c intervals were normal during the early stage of scarlet fever, became prolonged for a varying period and then returned to normal. Three of these patients had mild, nonmigratory arthralgia, and in 4 apical systolic murmurs developed. In none of these 10 cases could the presence of rheumatic fever be established on the basis of the criteria ap-

TABLE 2. *Data in 12 Patients Suspected of Having Rheumatic Fever (1946).**

Finding	No. of Patients
Age 3-5 yr.	4
Age 6-16 yr.	7
Age 31 yr.	1
Sore throat for 48 hr. or less before therapy	11
Fever during rheumatic activity	7
Increased PR & QT intervals	11
Arthralgia (nonmigratory)	3
Apical systolic murmur	4
Aortic diastolic murmur (normal electrocardiogram)	1
Migrating polyarthritis, cardiomegaly and apical diastolic murmur, with prolonged PR & QT intervals	1
Increased antistreptolysin titer	4
Increased antistreptokinase titer	2
Increased sedimentation rate	1

*Average latent period, 9.2 days

plied by the Air Force Research group.[2-4] The diagnosis was based primarily on the demonstration of prolongation of atrioventricular conduction, which appeared after a latent period.

Of the 12 patients in whom rheumatic fever was thought to have developed only 1 had had symptoms of pharyngitis for more than forty-eight hours before penicillin therapy was begun. Group A streptococci were isolated from the respiratory tract in every case. Four of the patients were three to five, 7 were between six and sixteen, and 1 was thirty-one years of age. The occurrence of rheumatic fever has been associated by some investigators with the persistence or reappearance of streptococci in the respiratory tract. In this group of cases, 7 patients were free of demonstrable streptococci at the time rheumatic fever was first suspected. In 3 the organisms reappeared in the pharynx at various intervals after cessation of penicillin treatment; in all these cases, however, the diagnosis of rheumatic fever was made before the bacteriologic recurrence, and in no case did pharyngitis recur. In 1 patient a bacteriologic but not clinical relapse was evident before manifestations of the rheumatic state occurred.

Only 4 of the 12 patients suspected of having rheumatic fever had a rise in antistreptolysin O titer; 2 showed an increase in antistreptokinase, and 1 had significant quantities of both antibodies. Only 1 had an elevated sedimentation rate during the period when he was thought to have acute rheumatic fever.

Most of the entire group of patients and all those who were suspected of having acute rheumatic fever were seen at weekly or biweekly intervals for three to six months after discharge from the hospital. At each of these visits a detailed history concerning recurrence of symptoms of pharyngitis or manifestations of rheumatic fever was obtained, a physical examination was performed, blood counts and urine studies were carried out, the erythrocyte sedimentation rate was determined, blood was drawn for serologic study, the nose and throat were cultured, and an electrocardiogram was taken. It has been pointed out in the Air Force studies[2,3] that episodes of rheumatic fever occurring thirty-five or more days after a penicillin-treated streptococcal infection do not result from this attack but are probably related to a later streptococcal infection that is undetected and therefore untreated. It is important to emphasize, for this reason, that in none of the patients in our 1946 study did evidence of rheumatic fever appear for the first time in the follow-up period. Thus, the rheumatic valvular disease observed seven years later in some of these cases was not due to an undiscovered streptococcal infection that occurred during the first six months after the patients were treated for scarlet fever.

Observations Made in 1953

One hundred and ten of the 167 patients treated in 1946 returned for study in 1953. Of these, 100 had had normal or "borderline" electrocardiograms, with no clinical manifestations of the rheumatic state, and 10 had been suspected of having had rheumatic fever seven years earlier.

Of the 100 patients who were not considered to have had rheumatic fever in 1946, 44 were found to have Grade 1 or 2 apical or precordial systolic murmurs, 23 exhibited a third heart sound after exercise, 19 had pulmonic systolic murmurs, and 33 revealed no abnormal cardiac sounds in 1953 (Table 3). Cardiac enlargement or other evidence of heart disease was not demonstrable by fluoroscopic examination in this group. On the basis of these findings it was concluded that none of these patients had detectable rheumatic heart disease.

TABLE 3. *1953 Follow-up Study of Patients with Normal or "Borderline" Electrocardiograms in 1946.*

FINDING	NO. OF PATIENTS
Grade 1 or 2 apical or precordial systolic murmur	44
3d heart sound after exercise	23
Pulmonic systolic murmur	19
No abnormal cardiac sounds	33
Negative fluoroscopic cardiac examination	100
Rheumatic heart disease present	0

None of the 10 patients who had been suspected of having rheumatic fever in 1946 gave a history of any illness resembling an attack of this disease in the following seven years; chemoprophylaxis was not given in any case. Although 2 had had episodes of pharyngitis that had been treated with one or another antibiotic agent, no recognized sequelae to these infections had developed. All those who were studied in 1953 had shown prolongation of the PR and QT intervals in 1946; 1 was a young woman who had had definite rheumatic fever with migrating polyarthritis, cardiomegaly, changing cardiac murmurs and prolonged conduction time seven years earlier. The patient in whom the diagnosis of rheumatic fever had been made seven years earlier on the basis of apical systolic and aortic diastolic murmurs was not seen in 1953 because he had moved away from New England.

The data obtained in the study of these 10 cases are presented in Table 4. Physical examination and roentgenographic study revealed findings consistent with rheumatic heart disease in 6. Four patients had mitral systolic and rumbling, low pitched mitral diastolic and presystolic murmurs. The fifth had mitral systolic and rumbling diastolic murmurs, as well as a blowing, decrescendo, diastolic murmur heard best along the left border of the sternum. In the 6th, mitral diastolic and systolic murmurs and a Grade 2 aortic systolic murmur were present. Roentgenographic study revealed a straight or convex left cardiac border in all patients; in 3 indentation of the esophagus by the left atrium was demonstrable after a barium swallow. Thus, 4 of this group of 6 had mitral insufficiency and stenosis, and 2 had involvement of

both the mitral and aortic valves. The ages of these patients in 1946 were four, five, seven, eight, sixteen and thirty-one years respectively.

Two other patients who had had abnormal electrocardiograms in 1946 were classified as having "probable" rheumatic heart disease in 1953. One was a thirteen-year-old boy (age six when treated for scarlet fever) who had a Grade 2 apical systolic murmur and enlargement of the left atrium without indentation of the esophagus on fluoroscopy; no diastolic murmurs were heard. The other was twenty-three years old in 1953, and x-ray study showed a straight left cardiac border and encroachment on the retro-

TABLE 4. *1953 Follow-up Study of Patients with Abnormal Electrocardiograms in 1946.**

FINDING	NO. OF PATIENTS
Patients with definite rheumatic heart disease:	
Mitral systolic, diastolic & presystolic murmurs	4
Mitral systolic & diastolic combined with aortic diastolic murmurs	1
Mitral systolic & diastolic combined with aortic systolic murmurs	1
Indentation of esophagus by left atrium	3
Straight or convex left cardiac border	6
Patients with "probable" rheumatic heart disease:	
Straight left cardiac border, Grade 3 mitral systolic murmur, encroachment on retrocardiac space & pulmonic 2d sound greater than aortic (age 23 yr.)	1
Grade 2 apical systolic murmur combined with enlargement of left atrium	1

*No rheumatic heart disease found in 2 patients on examination in 1953.

cardiac space; a Grade 3 apical systolic murmur transmitted to the right and left and a second pulmonic sound of greater intensity than the second aortic sound were also present. This young woman was the sister of the patient described above in whom aortic regurgitation and mitral insufficiency and stenosis followed prolonged atrioventricular conduction after an episode of penicillin-treated scarlet fever seven years previously. It is very likely that rheumatic heart disease was present in both these cases. They have been considered as "probable" rheumatic heart disease only because the murmur of mitral stenosis could not be detected. Since more than seven years may elapse before the mitral diastolic murmur becomes apparent, follow-up study of these patients will be carried out again several years hence.

The 2 remaining patients who had had abnormal electrocardiograms in 1946 showed no abnormal cardiac findings by physical examination or x-ray study seven years later. They were considered to have entirely normal hearts.

DISCUSSION

The data presented above suggest that the development of rheumatic heart disease was not appreciably suppressed by the treatment of acute streptococcal pharyngitis with penicillin in the patients described. It appears, also, that the clinical features of acute rheumatic fever were so altered by antibiotic therapy of the initiating streptococcal infection that most of the striking manifestations of the rheumatic state did not develop; carditis, as evidenced mainly by prolongation of atrioventricular conduction, became the outstanding feature. That increase in the PR and QT intervals was of importance in the diagnosis of acute rheumatic fever in these cases is strongly suggested by the observation that none of the 100 patients who had had normal tracings in the acute and convalescent stages of scarlet fever gave any evidence of rheumatic heart disease seven years later, whereas 8 of 10 with prolonged atrioventricular conduction later had definite or "probable" rheumatic heart disease.

It is interesting to discuss some of the possible reasons for the differences in opinion regarding the suppression of rheumatic fever by penicillin therapy of streptococcal pharyngitis reached by Denny et al.,[2] Wannamaker and his co-workers[3] and Weinstein, Bachrach and Boyer.[6] One very striking difference is the age of the patients treated. In our study the cases were, for the greatest part, in the age group in which the susceptibility to acute rheumatic fever is the highest. In the Air Force investigations,[2,3] on the other hand, all the subjects were in their late teens or twenties and so had been exposed to the possibility of getting rheumatic fever an unknown number of times before they were studied; thus, the older age and its accompanying decreased susceptibility may explain the relatively low prevalence of rheumatic fever in this group as contrasted to our patients, who were in the most susceptible age range. The control cases in the Air Force studies, however, exhibited the expected frequency of rheumatic fever, possibly because penicillin therapy is much more effective in suppressing rheumatic fever in those who are only slightly or moderately susceptible whereas, in highly susceptible children, such suppression may be incomplete and result in absence of the major manifestations, without a reduction in the occurrence of carditis.

One obvious difference between our first study and the investigations of the Air Force group[2,3] and of Massell and his co-workers[1] lies in the criteria used for the diagnosis of rheumatic fever. In our cases the possibility of rheumatic fever was suspected primarily on the basis of prolongation of atrioventricular conduction appearing after a latent period in persons who had at first a normal tracing and who, in every case, showed no electrocardiographic abnormalities in the recovery phase. In the other studies the diagnosis was made only if the criteria of Jones[4] were fulfilled. If we had applied the same basis for the diagnosis of rheumatic fever in our cases in 1946 a reduction in the frequency of this disease after the penicillin treatment of streptococcal pharyngitis would also have

been apparent. In the group of 167 patients only 2, or 1.2 per cent, had major manifestations of the type required to establish the presence of the acute rheumatic state according to Jones. This is a higher percentage than that reported by the Air Force group but lower than the number of cases of rheumatic fever (diagnosis based on Jones's criteria) observed in our clinic when streptococcal pharyngitis was not treated with penicillin — approximately 4 to 5 per cent. The lesser degree of reduction of clinically manifest rheumatic fever in our series when compared with others may be related to differences in susceptibility as influenced by age. It appears more likely to us, however, that the decrease in readily diagnosable rheumatic fever in this hospital since antibiotics have been used for the treatment of streptococcal infections is more apparent than real and can for the most part be accounted for by suppression of many of the common clinical features of the acute rheumatic state by therapy of the initiating pharyngitis; this would result in the detection of fewer cases of rheumatic fever since the criteria that had previously been of value would, in most cases, no longer be applicable. That this is probably true is strongly suggested by the demonstration of "probable" and definite rheumatic heart disease in 8 of 110 patients (7.9 per cent) who were studied seven years after treatment with penicillin for scarlet fever; the rate of proved rheumatic valvular disease in this group was 5.9 per cent. (These figures do not include the patient in whom aortic regurgitation without demonstrable electrocardiographic abnormalities developed after treatment in 1946; he could not return for follow-up study in 1953.) If the frequency of rheumatic heart disease detected in 1953 is calculated on the basis of the total of 167 patients included in our initial study (57 did not return for follow-up examinations seven years later) 7, or 4.2 per cent, had proved rheumatic heart disease (this includes the case in which aortic regurgitation developed in 1946), and 9, or 5.4 per cent, had "probable" or clear-cut rheumatic valvular involvement. This number of cases of rheumatic fever is little different from that observed by us in the preantibiotic era.

The question may be raised concerning the prevalence of rheumatic heart disease if a group of patients who received no antibiotic therapy for streptococcal pharyngitis were studied seven years later. As pointed out above, no untreated subjects were included in our 1946 study, and this question therefore cannot be answered. It appears, however, that the number of proved and "probable" cases of rheumatic heart disease observed by us in 110 patients in 1953 is comparable to that noted by many investigators in cases of streptococcal pharyngitis not given antibiotic agents. If, as has been claimed, penicillin therapy of streptococcal infection reduces the frequency of rheumatic fever, it must do so to a much lesser degree than has been suggested. If, as has been pointed out above, 6 to 8 (minimum of 4.2 to 5.4 per cent) patients with scarlet fever treated with penicillin have evidence of rheumatic heart disease seven years later the effect of antibiotic therapy of streptococcal infection in suppressing the development of this type of cardiac disease in children must be very small and may be of little clinical importance. The situation may be quite different in adults because of their lesser susceptibility to the development of rheumatic heart disease even when they have severe rheumatic fever.

It has been suggested[2,3] that the duration of pharyngitis before the initiation of chemotherapy is of importance in determining subsequent occurrence of rheumatic fever. In our 1946 study 57.6 per cent of the patients were given pencillin within twenty-four hours, and a total of 71.7 per cent received the drug within forty-eight hours or less after the appearance of the first symptoms of streptococcal pharyngitis. All the patients with evident or "probable" rheumatic heart disease in 1953 had been treated within forty-eight hours or less of the beginning of the sore throat seven years earlier. The importance of the period between beginning of infection and treatment has recently been questioned by some of the investigators who first stressed its importance. Catanzaro et al.[7] stated that "rheumatic fever was prevented when penicillin therapy of streptococcal pharyngitis was delayed until nine days after the onset of illness."

In that report[7] the development of antistreptolysin O was not suppressed and bore no relation to the appearance of rheumatic fever. This observation does not confirm previous suggestions[2,3] that the prevention or development of rheumatic fever can be correlated with the frequency and height of the antistreptolysin O titer. It is similar to the findings of Weinstein, Bachrach and Boyer,[6] who described elevations of antistreptolysin in only 5 of the 12 patients suspected of having acute rheumatic fever in 1946. The quantity of this antibody was not increased in the 2 patients in whom the diagnosis of rheumatic fever was established on the basis of Jones's[4] criteria. Suppression of formation of antistreptolysin O is related to the quantity of antibiotic given; rapid eradication of the organisms leads to failure of this antibody to increase above normal levels.[6]

Wannamaker and his colleagues[3] and Houser et al.[5] have noted that diagnosable episodes of rheumatic fever occurring after pencillin treatment are most apt to develop more than thirty-five days after therapy has been stopped, suggesting that these attacks are the result of a new infection with the beta-hemolytic streptococcus rather than being sequelae of the initial pharyngitis for which the antibiotic was given. In our patients, of whom all were followed in 1946 for a minimum of three and many for six months, rheumatic fever occurred within twenty-one days of the onset of the treated streptococcal infection; no case of this disease occurred during the fol-

low-up period. Persistence of streptococci in the pharynx has been associated by some investigators with the development of rheumatic fever. Of the patients found by us to have rheumatic heart disease in 1953, all but 1 were free of streptococci, as demonstrated by repeated cultures of the respiratory tract in 1946 when the presence of rheumatic fever was first suspected. One patient had a bacteriologic recurrence, before the appearance of suspected rheumatic fever, while he was still in the hospital.

It is essential to evaluate properly the significance of electrocardiographic changes in the diagnosis of rheumatic fever. Jones[4] pointed out that such abnormalities constitute only a minor criterion. Prolongation of the PR or QT interval or both is of greater significance than other abnormalities in suspected rheumatic carditis. Minor T-wave changes are of little or no importance because these are often related to fever or tachycardia or both. Furthermore, unless the prolongation of conduction time can be associated with a specific disease, the relation of even this abnormality to the diagnosis of acute rheumatic fever may be questioned. Prolongation of atrioventricular conduction has been observed, for example, in measles,[9] poliomyelitis[10] and diphtheria[11] among other infections.[12] However, increased PR and QT intervals occurring in cases of proved streptococcal infection appear to be diagnostic of acute rheumatic carditis. That this is probable is indicated by the fact that only patients who exhibited this type of electrocardiographic change after penicillin treatment of scarlet fever in 1946 had rheumatic heart disease seven years later. Despite the fact that it may not be possible in every case to attach clear-cut diagnostic significance to prolonged conduction, the data presented suggest strongly that this type of electrocardiographic abnormality is of more than minor importance and may, in fact, merit reconsideration as one of the major criteria for the diagnosis of rheumatic carditis in patients with proved streptococcal infections.

A question may be raised concerning the possibility that the patients who had valvular heart disease in 1953 experienced one or more episodes of acute rheumatic fever in the preceding seven years, despite the absence of a history of any such episodes. If this is so, the fact that not a single person with a normal electrocardiogram in 1946 later showed any evidence of rheumatic heart disease is impossible to explain unless, by some most unusual circumstance, only those with prolonged PR intervals in 1946 had unrecognized rheumatic fever in the following seven years. If, as a result of some peculiar accident, this did occur, however, the importance of the electrocardiogram is not decreased since the least that it accomplished was the detection of the patients who were most susceptible to the later appearance of rheumatic carditis and chronic valvular disease. Such an explanation for the presence of rheumatic heart disease seven years after the demonstration of prolonged atrioventricular conduction seems most unlikely and is very difficult to accept. All the data available point much more strongly to the fact that the abnormal electrocardiogram in 1946 resulted from acute rheumatic carditis, which led, in 80 per cent of the cases, to the subsequent development of chronic valvular disease.

Summary and Conclusions

A group of 110 patients with scarlet fever treated with penicillin in 1946, 100 of whom showed normal electrocardiograms and 10 prolongation of conduction after a latent period, were restudied in 1953. None of those without electrocardiographic changes in 1946 had any evidence of cardiac disease in 1953. Of those with prolonged PR and QT intervals seven years earlier 8 (7.9 per cent) had definite or "probable" rheumatic heart disease. In 6 (5.9 per cent) mitral insufficiency and stenosis were present; 2 of these had aortic as well as mitral lesions.

The data presented suggest that penicillin therapy of streptococcal pharyngitis in children, even when applied early, may not significantly decrease the occurrence of acute rheumatic carditis.

In children the clinical features of the acute rheumatic state may be markedly suppressed by the chemotherapy of the initiating streptococcal infection so that most or all of the characteristic signs and symptoms are absent and electrocardiographic evidence of carditis becomes the most prominent and sometimes the only diagnostic feature. Because of this it is probably necessary to redefine the present criteria for the diagnosis of acute rheumatic fever, particularly for children with antibiotic-treated streptococcal pharyngitis.

Demonstration of prolonged atrioventricular-conduction time, after a latent period, probably is highly significant for the diagnosis of rheumatic carditis in the absence of "major" manifestations if the patient can be proved to have had a recent streptococcal infection.

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EFFECTS OF LARGE DOSES OF CHLORAMPHENICOL ON HUMAN SUBJECTS*

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WHEN chloramphenicol first became available for general use in 1948, as one of the earliest broad-spectrum antibiotics, it was regarded as an important contribution to the treatment of infectious diseases. During 1950-52, however, numerous reports[1-16] appeared suggesting a relation between the administration of chloramphenicol and the development of aplastic anemia and pancytopenia. A direct causal relation could not be established in most of the cases, but considerable alarm was engendered concerning the hazards of using this drug.[17-20] This attitude toward chloramphenicol has recently been somewhat modified. It was estimated that 8,000,000 Americans had received chloramphenicol before 1953 without increase in the frequency of blood dyscrasias.[21] Lewis et al,[22] in a statistical review, found that although the number of blood dyscrasias had risen somewhat in that period, the increase occurred in patients who received no chloramphenicol as well as in those who had. In a recent extensive survey Welch, Lewis and Kerlan[23] reported that the frequency of hematologic depression related to chloramphenicol was low and that most of the suspected cases were poorly documented. Nevertheless, they suspected a relation and continued to advise caution in the use of the drug.

Thus, although the evidence is not clear, chloramphenicol is considered by most workers as a hazardous agent that may produce severe bone-marrow depression and should be used only in circumstances in which highly specific indications exist and in which the possible beneficial effects of the drug outweigh the potential hazard of bone-marrow depression.[24,25]

It was not clear from any of the reported cases whether the suggested toxic effects of chloramphenicol on the bone-marrow were due to a regular depressant action or to a "sensitization" reaction in the occasional person. Most authors believed that the latter possibility was more likely on the assumption that prolonged or intermittent therapy favored the production of bone-marrow damage.

This study was undertaken to investigate the effects of large doses of chloramphenicol in patients with neoplastic diseases, since if this drug were a consistent bone-marrow depressant it might have therapeutic effects similar to those observed with other regular bone-marrow depressants, such as nitrogen mustard, 6-mercaptopurine and the folic acid antagonists, and might therefore be useful in certain forms of neoplastic disease.

METHODS

Four patients with inoperable and far-advanced cancer were treated with chloramphenicol by mouth. The diagnoses were as follows: carcinoma of the vagina, with local extension; perithelial sarcoma, with cerebral invasion; melanocarcinoma, with widespread metastases; and carcinoma of the breast, operated and nonrecurrent, and carcinoma of the rectum, with abdominal and cerebral metastases.

The dosage was begun at conventional levels and then gradually increased until the maximum tolerated dose was achieved. The patients were observed frequently for any manifestations of toxicity and therapeutic effects. Hematologic studies consisted of daily hemoglobin, leukocyte and reticulocyte determinations. Differential leukocyte counts and platelet and erythrocyte counts were performed two or three times weekly. Bone-marrow examinations before, during and after treatment were performed on 3 of the 4 patients.

RESULTS

The dosage data and toxic effects are summarized in Table 1.

In Cases 1, 2 and 3 the limiting factor in the dose that could be given was glossitis. The tongue in these patients was characteristically reddened, edematous, smooth and very painful. Similar changes were seen in the buccal and pharyngeal mucosas. When the drug was stopped these signs disappeared in three to five days. Tongue and mucosal changes were produced a second time in Cases 1 and 3 after large doses were given. The photographs of the tongue in Case 3 (Fig. 1), which were taken before and during the second course of chloramphenicol, are representative of the changes occurring in all 3 patients. Mod-

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erate nausea and vomiting occurred in each case at high dosage levels only. These symptoms interfered with food intake and made it necessary to discontinue administration of chloramphenicol. With the exception of moderate weight loss in Case 1 during the second course of chloramphenicol therapy, there was no appreciable loss of body weight during treatment.

drug administration. Case 3 was discharged from the hospital to another city, so that the course of his anemia could not be followed.

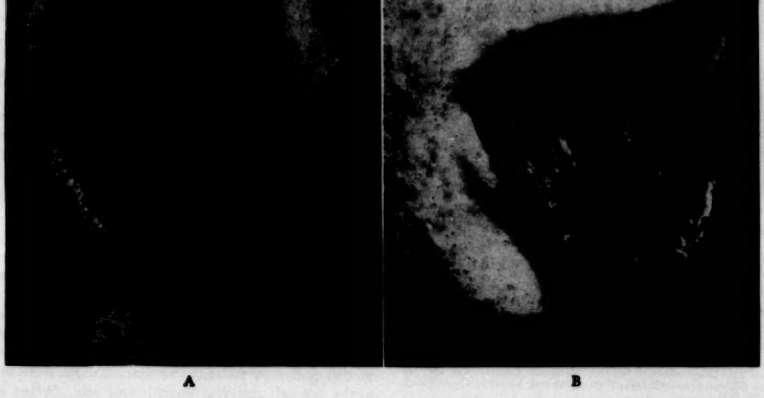
No changes occurred in the other parameters of evaluation in Cases 1, 2 and 3. No therapeutic effects on the neoplastic diseases were noted.

The observations on Case 4 are shown in detail in Figure 2. This patient was comatose because of hemorrhage into cerebral metastases and received both nutrition and medication via a stomach tube. Food intake was therefore constant during the period of observation. Tests of hepatic and renal function were

TABLE 1. *Dosage and Hematologic Data of Patients Treated with Chloramphenicol.*

CASE NO.	MAXIMUM DAILY DOSE	TOTAL COURSE		RETICULOCYTES*	HEMOGLOBIN	PLATELETS	WHITE-CELL COUNT	BONE MARROW	GLOSSITIS	ANOREXIA & NAUSEA
		DURATION	DOSE							
	gm.	*days*	*gm.*	%	*gm./100 cc.*					
1	8	18	93	0.5→ 0	17.7→12.7	No change	No change	No change	Severe	Moderate
	6	29	71	1.0→ 0	No change	No change	No change	No change	Severe	Moderate
2	12	35	161	0.5→ 0	14.5→ 9.0	No change	No change	—	Severe	Moderate
3	6	12	54	1.3→0.2	No change	No change	No change	No change	Severe	Moderate
	6	10	47	2.2→0.1	11.0→ 8.0	No change	No change	No change	Severe	Moderate
4	12	22	184	1.3→ 0	13.0→ 6.5	100,000→40,000	10,000→1,900	Change	None	None
	12	20	168	1.0→ 0	11.0→ 8.0	200,000→ 7,000	(See text)	Change	None	None

*Lowest values reported those persisting for at least 3 days & in Cases 1 and 4, for 8 consecutive days.



A B

FIGURE 1. *Appearance of the Tongue in Case 3 before* (A) *and during* (B) *the Second Course of Chloramphenicol Medication.*

Significant reticulocytopenia occurred in each patient. When the drug was discontinued the reticulocytes rose to higher than control levels in each case.

Hemoglobin levels decreased in all patients. In Cases 1 and 2 the anemia improved after cessation of

within normal limits. She received the largest dose of chloramphenicol administered in this series. Severe leukopenia, reticulocytopenia, thrombocytopenia and anemia developed, all being reversible when the drug was stopped. Subsequent administration of a single test dose of 0.5 gm. produced no hematologic abnormality, nor did administration of 2.0 gm. daily

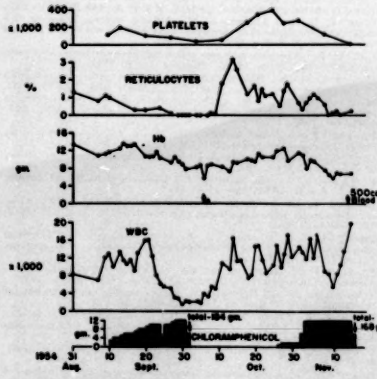


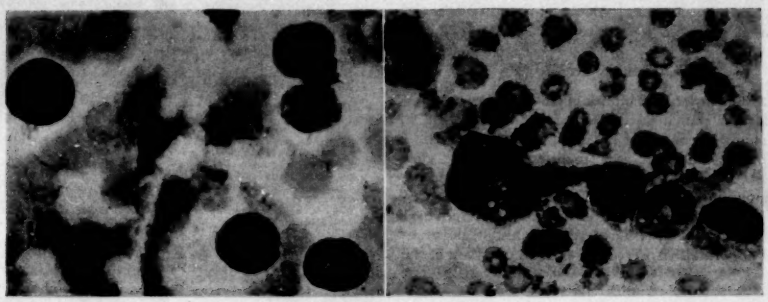
FIGURE 2. *Hematologic Data in Case 4 (a Forty-Six-Year-Old Woman with Carcinoma of the Breast and Rectum) during Two Courses of Chloramphenicol Therapy.*

for seven days. Readministration of large doses again caused a depletion of all cellular elements of the blood. The terminal leukocytosis in this case is thought to have been due to the myocardial infarction that occurred in the last forty-eight hours of life and was the cause of death. Differential leukocyte counts were unchanged throughout the course. The original bone-marrow examination was normal. A specimen at the time of the hematologic depression revealed no changes in the proportion of cellular elements. However, the cells of the myeloid series were abnormal in that they contained numerous cytoplasmic and nuclear vacuoles (Fig. 3). These vacuoles disappeared with recovery and recurred at the time of the second episode of hematologic depression. This patient, who received the largest total dose, did not have glossitis. Autopsy showed multiple metastases from the rectal carcinoma and a recent myocardial infarction. There were no specific lesions attributable to chloramphenicol, and the bone marrow disclosed normal cellularity.

DISCUSSION

Agents that depress the bone marrow may be divided into two groups. The first consists of agents with a direct, consistent action; for example, *polyfunctional alkylating agents* (nitrogen mustard, triethylene melamine and related compounds and myleran), *folic acid antagonists* (aminopterin and amethopterin), *purine analogues* (6-mercaptopurine, thioguanine, 6-chloropurine and 2,6-diaminopurine), *x-rays and radioactive isotopes* and *miscellaneous compounds* (benzene and urethane). The agents regularly produce bone-marrow depression when given in adequate dosage. Even with the drugs that consistently depress hematopoietic function a wide variation in individual susceptibility may be observed; the folic-acid antagonists, for example, may cause bone-marrow depression in certain patients at dosage levels far below those required in others.[26]

The second group consists of drugs that damage the bone marrow because of an individual idiosyncrasy to one of these substances; examples include Aminopyrine, thiouracil and related compounds, quinidine, gold preparations, Sedormid and Butazolidin. For inclusion in this group it must be demonstrated that a single dose of the agent can depress the peripheral



A B

FIGURE 3. *Bone-Marrow Aspirations in Case 4 before* (A) *and at the Conclusion of* (B) *the First Course of Chloramphenicol Therapy.*

blood count either with or without a prior "sensitizing" course of the drug. This has been demonstrated frequently with aminopyrine[27] and infrequently but definitely with quinidine.[28,29]

Under the conditions of this investigation chloramphenicol, when given in doses far in excess of those recommended for clinical use, appeared to fall into the group of drugs capable of producing some degree of impairment in hematopoietic activity.

In patients in whom some depression of the formed elements of the blood had resulted from large doses of chloramphenicol, hematologic idiosyncrasy did not appear when small doses were readministered. This argues against the concept of drug idiosyncrasy as a mechanism of hematologic depression in these patients. Our limited series does not, of course, rule out that possibility in other cases, but, as Welch, Lewis and Kerlan[23] point out, careful review of the published cases does not reveal any in which blood counts were done immediately before the dose of chloramphenicol thought to have caused a disturbance; thus, proof of drug idiosyncrasy is lacking. Our data indicate that a fall in the reticulocyte count is the earliest sign of bone-marrow intoxication, a conclusion previously drawn by Ley,[30] and, in selected patients receiving large doses or a prolonged course of chloramphenicol, reticulocyte counts may provide a useful means of hematologic control.

The oral lesions seen in our patients have much in common with those produced by azaserine[31] and the folic acid antagonists,[26] as well as those seen in pernicious anemia and certain vitamin deficiencies. The mechanism of action of chloramphenicol is not understood. Woolley[32] has suggested that it functions as an antimetabolite in relation to phenylalanine. However, this concept is not widely accepted and its significance regarding human toxicity is questionable.

Summary

Massive doses of chloramphenicol were administered to 4 patients with far-advanced cancer. No effects on the courses of the diseases were observed.

Minor hematologic abnormalities and severe glossitis occurred in 3 patients, the glossitis preventing continuation of the drug. Severe hematologic depression and bone-marrow abnormalities occurred in 1 patient, who tolerated larger doses without glossitis.

All abnormalities were reversible on cessation of the drug.

In 3 patients idiosyncrasy to chloramphenicol could not be demonstrated, and they tolerated large doses when chloramphenicol was readministered.

We are indebted to Dr. Allyn B. Ley for his help in evaluating the bone-marrow slides.

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DEVELOPMENTS IN ROTARY ABRASIVE TECHNICS FOR REMOVING ACNE SCARS AND OTHER COSMETIC DEFECTS

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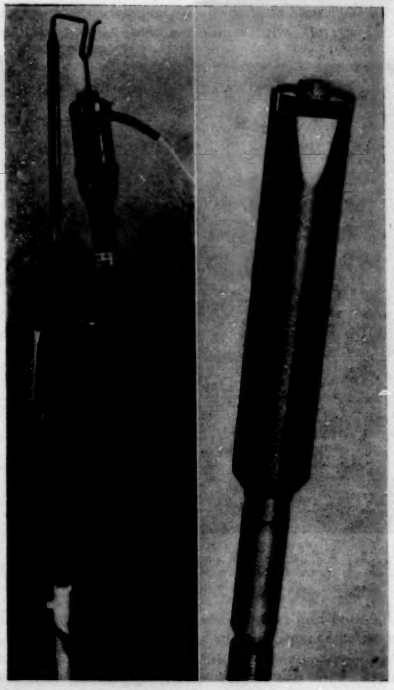
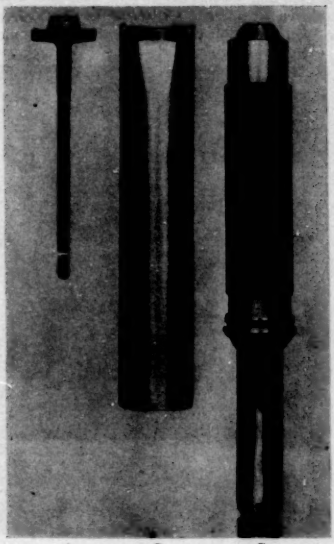
THE high-speed rotary abrasive technic has proved to be the most efficient procedure for removing pitted scars from acne, furuncles and smallpox, as well as those from certain traumas, and also for the removal of tattoos, pigmentations, certain nevi, keratoses and rhinophymas. For these cases the following different types of rotary abrasives have been used: heatless stones, steel burrs, steel-wire brushes and diamond and ruby fraises powered by high-speed rotary motors.



A B

FIGURE 1. *Schreus Apparatus* (A), *with Protective Sleeve over Handle and Grinding Stone Ready for Use* (B). *The motor is capable of 30,000 r.p.m. The flexible shaft, handle and stone grinder are enclosed in a protective sleeve. (This apparatus has a foot control.)*

The recent improvements in apparatus and technics, combined with the use of the newer local anesthetics, have made this method simple and safe. No hospitalization is required, and the procedure can be carried out with ease in the operating room of the physician's office. The patient may go home after the operation and return daily to have the dressings changed for a period of five or six days. Complete epithelization, with no visible scar, usually takes place within fourteen days of the operation.



A B C

FIGURE 2. *Heatless Stone Grinder and Adapter* (A), *with Protective Sleeve, Which Fits over the Handle and Grinding Stone to Prevent Spattering* (B) *and Handle on the Flexible Revolving Shaft* (C).

Kromayer,[1] in 1905 and later in 1933[2] and 1935,[3] was the first to report the use of motor-powered rotary steel burrs to produce dermal abrasion for the removal of pitted acne scars and tattoos, as well as many other skin blemishes. He was also the first to use ethyl chloride sprays for refrigeration anesthesia and for hardening the skin for dermal abrasion. Kromayer found that a rigid skin ground more easily with the low-velocity motors he used at that time. He reported good cosmetic results.

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In 1935 Janson[4] described the removal of tattoos by means of a hand-powered wire brush. He used sandpaper under general anesthesia for correcting scars on the face, and small motor-driven disks for lesions located in areas not easily accessible for sandpapering.

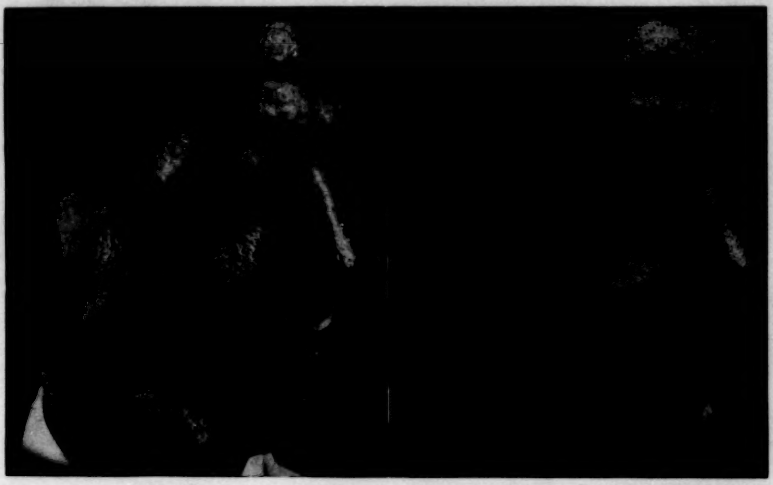
Schreus,[5] at a Congress held in 1949 in Heidelberg, reported excellent cosmetic results obtained by a high-speed rotary abrasive apparatus that he had designed, having a velocity of 30,000 r.p.m. He used stone grinding wheels of various sizes and a protective sleeve to prevent spattering of the ground tissues. With this high-velocity apparatus he found procaine-Corbasil local anesthesia most satisfactory for dermal abrasion.

Since Schreus's demonstration in 1949 and his published report in 1950,[6] various European[7,8] and American[9-12] dermatologists have presented their results with the Kromayer abrasion technic, the differences being in velocities of the motors and in types of abrasives, which included steel burrs, heatless stone wheels, steel brushes and diamond and ruby fraises.

I have previously reported[10] 200 cases treated by rotary steel-wire brushes with a velocity of 12,000 r.p.m. under ethyl chloride refrigeration anesthesia in which good cosmetic results were obtained. However, certain disadvantages with this technic were found. The tendency to profuse bleeding in the area treated masked the field of operation, making it difficult to obtain a uniform depth of abrasion. For the removal of tattoo marks the rotary steel-wire brushes were unsatisfactory because the pigment collected between the bristles of the brushes, with the possibility of its being ground back into the tissues. Consequently several brushes had to be used during an operation. Heatless stones were more satisfactory for tattoo marks because they were easily kept clean, even during the operation; they were also easier to guide and allowed the operator to see the skin planed away layer by layer, especially with the higher-velocity apparatus (30,000 r.p.m.).

I have used the Schreus high-speed apparatus (30,000 r.p.m.) with heatless stones, steel burrs and diamond and ruby fraises in hundreds of cases, with most satisfactory results. In a large number of these cases procaine-Cobefrin local anesthesia was used since, with this higher-velocity apparatus, it is not necessary to harden the skin by freezing. (Cobefrin constricts the blood vessels in the skin without cardiac effects.) Procaine anesthesia has certain advantages—for example, the field is always visible and not disguised as by freezing. The operator can see the skin abraded away layer by layer. The heatless stone grinders with a velocity of 30,000 r.p.m., used in conjunction either with procaine-Cobefrin local anesthesia or with refrigeration anesthesia, give a much smoother grinding than the steel-wire brushes with the lower speed of 12,000 r.p.m.

For the average case of acne scars, one dermal abrasion, done with the Schreus apparatus and stone



A B

FIGURE 3. *Appearance of a Male Patient with Acne Scars of Eighteen Years' Duration before* (A) *and after* (B) *a Single Dermal Abrasion by High-Speed Heatless Stone Grinders with Freon, a New, Noncombustible Refrigerant As Anesthetic.*

grinders, was usually sufficient for a satisfactory result. For the more severe and deeper pitted scars, a second and even a third dermal abrasion was necessary. These could be repeated at intervals of five to six months.

The Schreus apparatus (Fig. 1*A* and *B*) consists of a flexible shaft, a hand piece, protective sleeve, foot control, heatless stones of various sizes and a motor capable of 30,000 r.p.m. For a large and easily accessible area, a grinding stone (Fig. 2*A*) 1.9 cm. in diameter is preferable, but for the smaller and more difficult facial contours, such as those around the eyes and nose, stones 0.9 cm. or less in diameter are used, for which there are correspondingly smaller protective sleeves.

Complete control of the rotary heatless stone grinder by the operator is necessary for good cosmetic results. With the thumb as a pivot the skin is stretched taut, and with very light pressure the area is abraded — a thin layer at a time — until the desired depth is reached. The abrasion is done at right angles to the rotation of the stone wheels. The protective sleeve (Fig. 1*B*), which collects the ground tissues and blood and prevents spattering, gives the operator a clear working field.

In my experience it has been easier to control the depth of abrasion with the firmer stones or steel fraises than with the steel-wire brushes. However, one must be careful in placing the grinders lightly on the area to be treated. Steel and stone burrs can be more easily cleaned and are much more durable.

I have also used diamond and ruby fraises with satisfactory results. These fraises, like the heatless stones, generate very little heat and have the advantage of producing a very smooth and fine grinding.

In cases in which refrigeration anesthesia is desirable, I prefer to use Freon Mixture,[13,14] a noncombustible, nontoxic and nonirritating refrigeration anesthetic. This is sprayed on in the same way as ethyl chloride. However, the Freon Mixture does not require a blower.

A B

FIGURE 4. *Appearance of a Male Patient with a Traumatic Scar on the Nose of One Year's Duration before* (A) *and after* (B) *Dermal Abrasion.*

A single dermal abrasion by the high-speed rotary heatless stone (30,000 r.p.m.) grinder was done under local anesthesia with procaine cobefrin.

Typical results are shown in Figures 3 to 5.

SUMMARY AND CONCLUSIONS

I have used rotary dermal abrasive technic in several hundred cases of pitted acne scars and various other cosmetic defects such as post-traumatic scars, tattoos, pigmentations and early rhinophymas. The heatless stones and diamond and ruby fraises, powered by a high-velocity motor capable of 30,000 r.p.m., gave a much smoother grinding, a more satisfactory dermal abrasion and better cosmetic results than the steel-wire brushes, driven by lower-velocity motors of 12,000 r.p.m.

When the high-speed (Schreus) grinders are used it is not necessary to harden the skin, and therefore it is possible to use procaine-Cobefrin local anesthesia. With this anesthetic the field is always visible and not disguised as by freezing, which is most advantageous when small lesions, facial contours, linear scars, pigmentations and tattoo marks are being abraded.

A B

FIGURE 5. *Appearance of a Female Patient with Acne Scars of the Right Side of the Face of Fifteen Years' Duration before* (A) *and after* (B) *a Single Dermal Abrasion with the High-Speed Rotary Heatless Stone Grinder under Anesthesia with Freon Mixture.*

In cases of dermal abrasion in which refrigeration anesthesia is desirable Freon Mixture is preferable to ethyl chloride, since it is nonexplosive and nontoxic. My experience with the use of Freon Mixture in large numbers of cases has proved it to be a safe and satisfactory refrigeration anesthetic.

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SUCCESSFUL EXCISION OF AN AORTIC ANEURYSM EXPLORED AS A PARASPINAL TUMOR*

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THE exact diagnosis of certain paraspinal tumors may be difficult. When usual means of diagnosis are exhausted, exploration and biopsy may offer the best means of indicating possible definitive treatment. The case reported below demonstrates some of the problems in diagnosis, even at the time of exploration. Hemorrhage from a biopsy of the wall of an aortic aneurysm was controlled, and the sac was resected successfully under emergency conditions.

CASE REPORT

H.M., a 49-year-old Negro chauffeur, was admitted to Presbyterian Hospital (Orthopedic Division) on January 14, 1953, because of low-back pain of 1 year's duration. The pain was present in the lower dorsal spine, in both costovertebral angles, and occurred without relation to motion or position. During the month immediately before admission this discomfort had radiated to the left iliac and inguinal regions. He had continued to have a good appetite and had lost no weight. He denied fever and night sweats; however, a chronic cough accentuated the discomfort. In December, 1952, he had been seen in an out-of-state hospital, where x-ray films of the spine showed moderate destruction of the 11th and 12th thoracic vertebras.

The past history revealed syphilis in 1936, for which he had received "several courses" of injections. A brother had died of pulmonary tuberculosis, but the patient had had little contact with him.

Physical examination disclosed a well nourished and well developed man who was in no acute distress. Positive physical findings included a soft systolic murmur, with an accentuated pulmonic 2d sound. The abdomen was not tender, and there were no palpable masses.

The temperature was 99.4°F, the pulse 112, and the respirations 20. The blood pressure was 150/95.

Orthopedic examination showed good posture and a normal gait. However, there was minimal tenderness over the left costovertebral angle. The alignment of the spine was good, and motion was painless and free. The tendon reflexes in all extremities were equal and brisk. There was a full range of motion in both hips. Motor power and arterial pulsations in both lower extremities were equal and of good quality.

X-ray examination of the chest revealed a normal heart; the lung fields were not remarkable. A mass protruded on both sides of the spine, superimposed on the cardiac shadow (Fig. 1).

X-ray films, including laminagraphy in the anteroposterior projection, showed a destructive process involving the bodies of the 11th and 12th dorsal vertebras, especially on the left. There was a narrowing of the intervertebral-disk space. A soft-tissue mass was associated with this process, extending much more to the left than to the right of the spine (Fig. 2). The radiographic impression was that this represented chronic infection, probably tuberculosis, the 2d most likely possibility being a chordoma.

The sedimentation rate was 3 mm. and 5 mm. per hour on 2 occasions. A tuberculin test was negative in 1:10,000 dilution. The white-cell count was 8800, with a normal differential, and the hemoglobin 13.7 gm. per 100 cc. Urinalysis was negative. An intravenous urogram revealed well defined psoas muscles and normal excretion from the kidneys, which were normal in size, location and shape. The nonprotein nitrogen was 30 mg., the acid phosphatase 1.7 Gutman units, the alkaline phosphatase 3.7 Bodansky units, the fasting serum calcium 11.2 mg., and the serum protein 7.1 gm. per 100 cc., with an albumin of 4.6 gm. and a globulin of 2.5 gm. per 100 cc. Mazzini tests were + and ++, and Kolmer tests were negative. The Venereal Disease Research Laboratory test was negative on January 6 and positive (undiluted) on January 15.

FIGURE 1. *Overexposed Roentgenogram of the Chest, Showing a Paraspinal Mass at the Level of the Diaphragm, behind the Cardiac Shadow.*

An electrocardiogram on January 23 revealed a sinus rhythm and a pulse rate of 90. The PR interval was 0.15 second. There was a right-bundle-branch block.

On January 16 a needle biopsy of the mass at the level of the 12th dorsal vertebra was performed under fluoroscopic control. Microscopical examination showed extensive old hemorrhage and fibrosis of bone marrow, bone necrosis and bone resorption, with bone repair. This was consistent with an old fracture with much hemorrhage and poor reparative reaction. Although Paget's disease could not be ruled out, the preferred clinical diagnosis was tuberculosis or neoplasm.

In view of the inability to reach a definite diagnosis, an exploratory operation was performed on February 4. With the patient in the right lateral decubitus position, a vertical incision was made over the 10th, 11th, and 12th ribs to the left of the spinous processes extending laterally beneath the 12th rib; segments of the 11th and 12th ribs were removed to permit an extrapleural approach to the large paraspinal tumor. The mass proved to have a grayish-white wall, did not pulsate and was intimately adherent posteriorly to the bodies of the 11th and 12th dorsal vertebras. After

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aspiration with several large needles inserted into the tumor had failed to produce pus or blood, a small longitudinal incision was made in the wall, and grayish-red, necrotic material was removed for frozen section. It was determined at this point that the posterior part of the wall of the tumor mass was fused to the bodies of the 11th and 12th dorsal

FIGURE 2. *Anteroposterior Laminagram at the 7-Cm. Level, Showing Marked Destruction of the Bodies of the Eleventh and Twelfth Dorsal Vertebras, with Narrowing of the Interspace.*

vertebras; the 12th appeared to have been deeply eroded, and the edges were rough and irregular. The orthopedic surgeon elected to add a portion of the necrotic bone for biopsy, and as a curette was inserted into this space, there was a sudden forceful gush of arterial blood from the site. The fact that the mass was an aneurysm of the aorta was immediately apparent. While control of the hemorrhage was effected by digital pressure on the biopsy site the vascular surgeons assumed the surgical responsibility.

The skin incision was extended both superiorly and inferiorly, and additional segments of the 9th and 10th ribs were resected so that the pleura could be reflected further superiorly and anteriorly. This afforded ample exposure of the aorta above, and a Bethune tourniquet could be placed about the aorta above the area of the aneurysm. This tourniquet was not compressed because the bleeding was under control by digital pressure. The lower limb of the incision was extended into the left anterolateral flank, where, after similarly the aorta had been isolated, another tourniquet was loosely applied about the aorta below the aneurysmal sac. With these tourniquets in place for control of aortic bleeding the mouth of the aneurysm was dissected from the contiguous aortic wall. It was then possible to place a sliding type of right-angle clamp across the mouth of the saccular aneurysm and to amputate the sac just distal to the clamp. The mouth, measuring 7 cm. in width, was then satisfactorily closed with interrupted mattress sutures of No. 00 braided silk, supplemented by a continuous suture of No. 000 braided silk (Fig. 3). The remainder of the sac was dissected from the surface of the eroded vertebral bodies posteriorly. The celiac axis and superior mesenteric artery arose from the aorta anterior to the aneurysmal orifice (Fig. 3).

Except for intractable hiccups in the first few postoperative days and left pleural effusion, the patient had an uneventful convalescence. He was discharged on the 14th day, wearing a Taylor back brace for support. He received a course of antibiotic therapy for the syphilis during his hospital stay.

He was free of all pain after about 6 months but continued to wear the brace and to use boards beneath his mattress. He returned to work as a chauffeur after about 6 months. Repeated x-ray examination of the spine revealed little change in the area of destruction as long as 21 months after operation. He had excellent motion in the spine at this time and had normal arterial pulses in the lower extremities. A slight scoliosis was present at the level of the bone changes. When last seen on May 20, 1955, he was comfortable and was working full time as a private chauffeur.

DISCUSSION

This case emphasizes the fact that aneurysm may masquerade as an inflammatory mass or neoplasm,

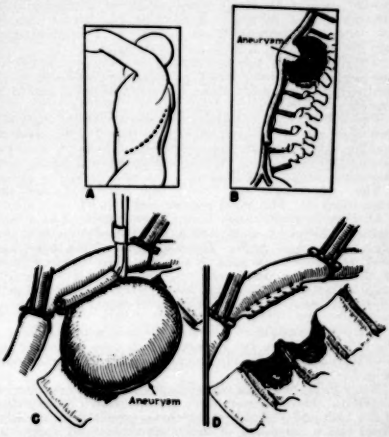

FIGURE 3. *Surgical Procedure.*

A=line of incision. B=diagrammatic representation of the aneurysm (the sac is almost entirely filled with clot). After application of tourniquets to the aorta, on each side of the aneurysm for hemostatic control, a Crump clamp was placed across the neck of the aneurysm (C). *After excision of the aneurysm the mouth was sutured firmly* (D). *It was not necessary to occlude the aorta during the procedure.*

especially when located in the posterior mediastinum or in the paraspinal region. Bone destruction, seen with syphilitic aortic aneurysm, is rarely observed with abdominal aneurysm, which is generally arteriosclerotic. An aortic aneurysm is uncommon in the supra-

renal portion of the abdominal aorta, but, when found there, it is of syphilitic origin, in general. Since these aneurysms occupy a posterior position bone erosion is often observed. Although the technics of laminagraphy and needle biopsy may yield sufficient information for a definite diagnosis, the true nature of the process in the case reported above was apparent only at operation.

Visualization technics in peripheral arteries have often been helpful to the orthopedic surgeon in his study of traumatic, cystic and neoplastic lesions involving the bones of the extremities. The recognition of a traumatic aneurysm of the leg by arteriogram in a patient suspected of having a bone sarcoma has been described by Bowie and Kay.[1] Although the thoracic aorta can be well delineated by angiocardiography[2] and the abdominal aorta by angiocardiography,[2,3] translumbar aortography[4] or retrograde aortography,[5] these methods are not generally employed by the orthopedic surgeon. The value of angiocardiography in differentiating certain mediastinal tumors has been well recognized.[2,6,7] The use of translumbar aortography as an aid in diagnosis of abdominal tumors and aortic aneurysms has also been reported.[8,9] It is possible that a translumbar aortogram in the posteroanterior projection would not have helped in the case reported above since only a small active sac existed, and this was directly posterior to the aortic channel. However, an angiocardiographic series in the lateral position probably would have disclosed the small communicating portion of the sac, as well as the anterior displacement of the aorta. More satisfactory preparations could then have been made for definitive surgery.

The success achieved in this case can be expected with this type of lesion, in which excision of the sac is usually quite satisfactory. Unlike the arteriosclerotic aneurysm the syphilitic type is a localized lesion, with reasonably normal aorta immediately adjacent to the aneurysm. However, Cooley and DeBakey[10] report the recurrence of an aneurysm in the region of a previously excised syphilitic saccular aneurysm of the lower thoracic aorta. This was later resected, and a homograft employed.

Ever since resection of the sac with maintenance of aortic continuity was proposed by Tuffier[11] few successful cases were reported until less than a decade ago. Individual cases were described by Blakemore,[12] Ochsner[13] and Meyer et al.[14] In the past few years, additional reports have been made by Cooley and DeBakey,[15-17] Bahnson,[18,19] Hardy[20] and Barnes and Yeager.[21] The aneurysm in Bahnson's second case was similar in location to that in the case presented above, and, although much larger, it was well demonstrated by retrograde aortography. Bahnson had advocated removal of all the clot and sac wall as a result of complications occurring in 1 of his patients when infection developed in a clot left behind. The sac wall may be too adherent or thickened for complete removal in some cases, and it should be noted that the thickened fibrous tissue forming the mouth of the sac in the case reported above necessitated use of heavier suture material than the usual No. 00000 braided arterial silk employed in vascular surgery.

In conclusion it seems wise to make wider use of visualization technics in the definition of mediastinal and paraspinal masses. In some cases the evidence may be equivocal even after such studies. If exploration and biopsy are performed it would be well to have at hand surgeons with vascular experience since the lesion may be an aneurysm. The successful management possible even under emergency circumstances is exemplified by this case.

Summary

A case in which a paraspinal tumor with vertebral erosion was believed to be a Potts abscess or a neoplasm is reported. Biopsy revealed the mass to be a syphilitic aortic aneurysm. It was possible to isolate the mouth of the sac and to resect the aneurysm successfully while bleeding was controlled from the biopsy site. The patient was free of pain and working for over two years after operation.

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MEDICAL PROGRESS

MALIGNANT MELANOMA

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PIGMENT cells, normal and abnormal, have been the subject of much recent biologic and chemical study.[1,2] This report summarizes such data, and in addition presents the current understanding of the genesis, diagnosis and therapy of the malignant melanoma.

MELANOCYTES

Melanin production occurs only in cells, normal or neoplastic, possessing the enzyme tyrosinase that catalyzes the reaction: tyrosine ⟶ melanin. Tyrosinase-containing cells have been demonstrated principally in the epidermis, eye and meninges; these areas are the most frequent locations of the malignant melanoma. Numerous explanations have been offered for the occurrence of melanin outside such sites, including the extracellular escape of late metabolites of tyrosine,[3] phagocytosis, metastatic extension, melanocytic heterotopia and questionable pigment transfer.

Melanoblasts, the precursors of the normal cells capable of melanin synthesis (melanocytes), originate from the neural crest, a transient dorsal embryologic structure of ectodermal origin, and then migrate to their final position in the basal layer of the epidermis.[4] In addition to work in experimental vertebrate embryology, evidence favoring the neural origin of melanocytes, rather than an epidermal genesis, has been summarized,[5] as follows:

> Melanocytes, like other nerve cells, are dendritic in shape.
>
> Methylene blue, silver and gold stain melanin-producing cells as well as other nerve tissues.
>
> Melanocytes produce dihydroxyphenylalanine, a compound related chemically to nor-epinephrine, a product of the sympathetic nervous system.
>
> Malignant tumors of these cells (maligant melanomas) do not respond to irradiation therapy and are similar to nerve cells in being relatively radioresistant.
>
> Pigmentation abnormalities are often associated with aberrations of the central nervous system (such as neurofibromatosis).

The origin of malignant melanocytes is unknown, but their precursors are also assumed to arise from the neural crest.

MELANOGENESIS

The chemistry of melanin formation has been advanced and clarified by the investigations of Lerner and Fitzpatrick.[6] Tyrosine, oxidized to dihydroxyphenylalanine by the copper-containing enzyme, tyrosinase, undergoes further oxidation to a quinone, which, after a series of rearrangements to an indole-like compound, polymerizes to form melanin. Precise structural formulation of the melanin polymer has not been achieved, and it is possible that two or more chemical characters are involved. The melanin of mammalian tissues is protein precipitable, and Sizer[7] has shown that tyrosinase acts on tyrosine residues within certain protein molecules. On electron microscopy, melanin occurs as discrete granules within the melanocyte; and Plummer and Kopac[8] partially reproduced these particles in vitro, noting that suitable tyrosinase substrates would attach themselves to starch granules.

Sulfhydryl groups, and other inadequately understood factors such as the cellular electromotive force, control melanogenesis in normal skin. Sulfhydryl binds the copper of tyrosinase, thereby inactivating the enzyme. Sunlight alters the cell potential, liberates the reaction from sulfhydryl domination and increases melanogenesis. Pigmented areas show a lower sulfhydryl content than surrounding skin sections, but whether a defect of sulfhydryl metabolism exists in malignant melanomas is unknown. With the possible exception of certain amelanotic variants the malignant melanoma possesses an active tyrosinase system that is independent of actinic stimulation. The tumor also demonstrates the presence of free tyrosine, but shows no increased uptake of radioactive copper.[9]

ETIOLOGY

An adequate hypothesis for the genesis of malignant melanoma must account for melanocytic neoplasia, rather than pigment production, since neither the tyrosine nor the melanin content of a melanoma is proportional to the malignancy of the lesion. This can be inferred from the following facts:

> Amelanotic melanomas are as malignant as their pigmented counterparts.
>
> Agents that depigment the tumor (tyrosinase inhibitors such as sulfhydryl groups and oxidation-reduction compounds like ascorbic acid) do not necessarily slow its growth.

Local irritation may correlate with tumor induction; 30 per cent of the patients with malignant melanoma in one series gave a history of preceding trauma to a mole. Further support for the injury theory is found in the observation that arsenic paint-

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ing in mice is accompanied by increased melanin accumulation locally,[10] and the late manifestations of arsenic administration in man often consist in darkly pigmented and hyperkeratotic skin lesions. Such melanization is compatible with the binding of tissue sulfhydryl groups by the heavy metal.[6] Although in the fruit fly (*Drosophila melanogaster*) a melanotic tumor is produced by the injection of acellular extracts of larval fluid into developing embryos,[11] there is little additional evidence to support a viral etiology. The pituitary melanocyte-stimulating hormone, or intermedin, can cause generalized melanosis. Whether its excessive endogenous production, or its exogenous introduction can result in neoplasia has not been determined.[12-14]

Laboratory Studies

Numerous phenolic compounds are synthesized by a malignant melanoma, and may find their way into the blood stream and be excreted by the kidneys before they can be converted to chromogenic molecules. The oxidation and escape of these substances is related to the relative amounts of the cytochrome-oxidizing and phenol-oxidizing enzyme systems present in the cellular mitochondria.[15] Occasionally, clinically inapparent malignant melanomas are detected by the excretion of a urine that turns black on standing, owing to oxidation of these moieties.

Part of the excreted fraction is composed of simple indole derivatives, or, collectively, "melanogen." Slow oxidation of these substances by air results in the characteristic black color. Attempts have been made to use more rapidly acting oxidants in the detection of melanogenuria. Commonly employed are ferric chloride (von Jaksch and Pollak) and bromine,[16] although they are nonspecific and relatively insensitive. According to Helman,[17] melanogen can be determined by the following procedures, all of which must be positive before the compound can be confidently considered to be present:

A brown precipitate forms on the addition of ferric chloride.

Sodium carbonate dissolves the precipitate, forming a black solution.

A black or brown precipitate occurs on the addition of mineral acid to the black carbonate solution.

In 1887 Thormählen[18] described a method that, with modification, has served as a sensitive, almost specific indicator of melanogen.[19] The procedure is similar to Legal's test for acetone: 0.3 cc. of diluted sodium nitroprusside is added to 5 cc. of urine, and this is followed by 0.5 cc. of 10 per cent sodium hydroxide. A ruby-red color occurs on alkalinization that is nonspecific (being given also by acetone and creatine). However, acidification with glacial acetic acid produces an immediate azure blue with melanogen (and with closely related indole derivatives); the reaction is about fifty times more sensitive than oxidation tests. Melanogenuria does not depend necessarily on hepatic damage by the pigment or tumor, since the ingestion of phenolic indole compounds by normal subjects is followed by melanogen in the urine.[20]

Melanogen, independently of urobilinogen, gives a positive Ehrlich aldehyde test.[21] The reaction can determine smaller quantities of melanogen than the Thormählen procedure, although separating the urobilinogen is not usually feasible. Experimentally, potato tyrosinase oxidizes tyrosine in urine,[22] and perhaps other phenolic compounds as well. This may prove of value clinically in the detection of such materials in the urine of patients before and after therapy for malignant melanoma.

Melanogen in urine is accompanied by a substance, probably the melanocyte-stimulating hormone, capable of increasing melanophore size in hypophysectomized frogs.[23] Increased urinary melanocyte-stimulating hormone is found in a number of other conditions, however, including Addison's disease, starvation melanosis and pregnancy. The administration of the hormone is associated with a rise in serum copper, and the triad of elevated serum copper, increased urinary melanocyte-stimulating hormone and hyperpigmentation has been termed melasma.

Clinical Aspects

Laënnec,[24] in 1806, reported the occurrence of a human melanotic tumor. Fifty-one years later, Moore[25] noted the first case involving the rectum, and in the same year Pemberton[26] pointed to the pigmented nevus as a precursor of malignant melanoma. Since then, amelanotic variants of the tumor have also been recognized.

Although encountered more frequently in elderly persons malignant melanomas occur in every age group. There is an equal distribution between the sexes. More often found in the fair skinned, the tumor is not uncommon in Negroes. Despite its notoriety, malignant melanoma accounts for less than 0.5 per cent of the yearly deaths from cancer. Primary malignant melanomas have a prevalence of 1.8 per 100,000,[27] and multiple tumors are common.[28]

Pigmented hairy moles and the numerous brown spots of the skin are usually benign, but the presence of hair should not be taken as a sign of absolute benignity.[29] Any melanotic site that rapidly increases in size, becomes more pigmented, cracks or weeps, shows satellite lesions or is associated with otherwise unexplained enlarged lymph nodes or pruritus must be considered already malignant, not as a lesion of precancerous potential that can be watched. Ulceration carries a particularly ominous outlook.[30] Suspicious nevi must be removed in toto and presented for microscopical analysis since no absolute criteria exist, except for histologic examination, for determining if neoplasia has occurred. In addition the extirpated lesion has no chance of recurring.

Because of the occurrence of amelanotic variants

and the frequent finding of pigment in other nevi, neoplasms and granulomas, a precise diagnosis depends on cytologic criteria. Since the most common problem is differentiating a benign nevus from a malignant one, the following description of nevi, adapted from Allen and Spitz,[31] is appropriate:

Intradermal Nevus

This, the common mole, never undergoes malignant changes. The presence of hair is presumptive evidence that the lesion is intradermal. It may occur at any location or age, but is rare on the soles, palms and genitalia, and uncommon before puberty. Histologically, the epidermis is intact, without junctional change. Occasional giant cells appear from the fusion of benign single nevus cells. Never encapsulated, it may extend into the subcutaneous fat.

Junctional Nevus

This is a definitely premalignant lesion. Pigmented blemishes on the genitalia, the soles of the feet and the palms are of this type, but the nevus may occur in any part of the skin surface or mucous membranes. It is hairless, smooth, flat to slightly raised and various shades of brown. When quiescent, the junctional nevus shows loss of cohesion of cells beginning with basal layers and progressing upward, vacuolization and loss of prickles of the involved epidermal cells and scattered to increased melanin pigmentation.

Compound Nevus

This consists of an intradermal nevus and an immediately overlying junctional nevus that are usually impossible to determine clinically. The junctional area is stated to undergo malignant change in 98 per cent of the compound nevi in children and in 12 per cent of those in adults.

Juvenile Melanoma

This lesion[32] is benign, and not a precursor of malignant melanoma. It constitutes 6 to 8 per cent of all pigmented nevi surgically removed from children, and rarely occurs in adults. The cells are large but lack the anaplastic changes seen in malignant melanomatous cells of this size.

Blue Nevus (Jadassohn—Tièche)

Much melanin, and its deep position in the dermis, result in the blue color. Occurring principally on the buttocks, the dorsum of the feet and hands and the face, it is brown to blue black and rarely trichotic, and may be associated with other nevi. Composed of compactly or loosely disposed spindle-shaped cells, the blue nevus often resembles the arrangement of smooth muscle or nerve.

Melanoma

A melanoma, superficial or deep, may arise from a junctional or compound nevus. Couperus and Rucker[33] concluded that the diagnosis of primary malignant melanoma could be made if one or more of the following criteria were present in addition to junctional changes; inflammatory infiltrate at the periphery of the lesion; more than an occasional mitotic figure; giant cells with a single bizarre nucleus; marked pleomorphism; general enlargement of all tumor cells; and tumor cells and mitoses in the epidermis.

Malignant Blue Nevis

A relatively rare lesion, but more common than true melanomas in children, this can be mistakenly diagnosed from spindle-cell melanoma arising from a junctional nevus, nonmalignant cellular blue nevus and spindle-cell metastases from a malignant melanoma.

In addition to routine hematoxylin-eosin staining of removed tissue, three technics may prove of value in the differential diagnosis of pigmented lesions.

Differential Stains

These help in the precise delineation of microscopic structure. Specific dyes can permeate cells surrounding the melanocytes,[34] color the melanocytes proper[35,36] or darken pre-existing melanin.[37-40] Other procedures demonstrate the presence of the dihydroxyphenylalanine-oxidase (tyrosinase)[36] and the conversion of tyrosine to melanin after actinic stimulation of skin sections.[41] Suitable technics of radioautography have not been reported.

Exfoliative Cytology

Wilson[42] proposed that touch smears of skin lesions, after biopsy, might have value as a diagnostic aid. Such a technic, or exfoliative cytology before biopsy, might be applied to forms of malignant melanoma in which cells are pushed upward instead of invading underlying structures.

Tyrosine Uptake

Reid and Jones[43] administered C^{14}-labeled tyrosine to melanoma-bearing mice and noted a slight uptake in the tumor. Poppe and Frädrich[44] also investigated the radioactive tyrosine concentration of recurrent malignant melanomas. These studies are of interest, but at present should not be expected to replace the more reliable histologic examination.

Primary and Metastatic Sites

A compilation of numerous large case studies indicates the following approximate distribution of the primary sites of the malignant melanoma: skin, 80 per cent; eye, 10 per cent; nervous system, 4 per cent; and other sites, 6 per cent.

The lower extremity, not a usual site for moles, is the commonest single location of the primary tumor and accounts for a third of the skin varieties. Such growths on the sole are easily visualized although

often confused with other lesions: those occurring between the toes may be overlooked. Malignant melanomas of the head and neck account for a fourth of the skin species, and subungual types are less than an eighth as common. Gastrointestinal varieties of this neoplasm are unusual, with only 4 authenticated cases in which the initial growth arose in the esophagus. In the rectum the involvement may be at or above the anal verge; rarely, the tumor will protrude, appearing very much like an internal hemorrhoid.[45] The bulbar conjunctiva, iris, choroid and uveal tract are sites of primary malignant melanomas of the eye although many benign melanotic tumors are also found in these locations. The central nervous system and its coverings are less common sites of the primary tumor.

From its initial location the growth spreads by blood and lymphatic channels to any part of the body; indeed, in some cases dissemination is so extensive that the initial focus may be indeterminate. A malignant melanoma frequently spreads to the brain and local lymph nodes (which may be more pigmented than the primary site). According to Bisel et al.,[46] of 34 patients with metastatic melanoma, 44 per cent showed cardiac involvement, skin and bone being the next most frequent secondary sites. Other series reveal that local lymph nodes, lung, liver and heart are often secondarily involved by the tumor. In one series 41 per cent of the males and 38 per cent of the females had metastases when the diagnosis was first established, and in a second independent report the figures were 64 per cent and 61 per cent.[47] One should therefore search carefully for metastases after a primary melanoma is located.

Clinical evidence of metastasis may be the first indication of the malignant process. However, long intervals occasionally occur between removal of ocular and other malignant melanomas and the observation of secondary spread. Factors initiating the emergence of long-dormant seedings remain unknown, but local trauma, tissue aging and other conditions have been mentioned. Unusual secondary sites also occur, and the transplacental transmission of a malignant melanoma has been reported.[48] Such an occurrence is so rare that there seems to be little reason to warrant terminating pregnancy; abortion does not slow the tumor growth. There is also a report of the development of the tumor in both donor and recipient areas of an autogenous skin graft.[49] Although genetic aspects of the inheritance of melanotic tumors in certain lower forms has been presented[50] no evidence of a hereditary transmission in man has appeared.

Therapy

It is not usually feasible or necessary to remove all pigmented nevi. However, moles in an area likely to be subjected to trauma should be prophylactically excised, especially if they are located on the palms, soles or genitalia (at which sites junctional nevi are more commonly found than intradermal nevi). A completely removed pigmented mole does not recur as a malignant melanoma, and if dissemination is later found, the mole was malignant initially.

Freezing, irradiating or electrolyzing pigmented areas should be abandoned in favor of complete and radical excision. Surgery of a malignant melanoma must be directed at complete removal of the primary focus at the first operation; reoperation, which is technically difficult, adds little to survival. Cutaneous malignant melanomas are excised with a wide margin of normal skin, care being taken not to disturb the pigmented site, and the dissection is carried down to the deep fascia (or beyond, if extension is visible). When the regional lymph nodes are in the same area a block operation seems desirable. Many nonenlarged regional lymph nodes can be shown microscopically to contain metastatic melanocytes; hence nodes must be dissected in all cases if feasible. With nodes far from the primary site the initial tumor may be removed in an attempt to prevent further seeding, and the nodes excised by radical block dissection after an interval.

Although malignant melanoma often pursues a fulminant course, being second only to chorioepithelioma in its pernicious nature, several varieties carry a relatively good prognosis. Pack et al.[51] reported over-all five-year survival without visible metastases in 21 per cent of treated cases (16 per cent in males and 27 per cent in females). Lowest survival rates occurred in cases of secondary lesions in which the primary focus could not be located during life, in oronasal types and in lesions of the trunk. At the other end of the scale, a more favorable outlook occurred with subungual and palmar foci, and with occasional ocular melanomas. According to Allen and Spitz[52] local recurrences or metastases to regional lymph nodes do not preclude survival, and five-year survival is by no means tantamount to cure. Whether radical amputation of an affected extremity more favorably influences survival than removal of the primary lesion and the affected lymph nodes is at present not certain.

Unfortunately, certain sites may not be amenable to surgical intervention. In such locations irradiation has been employed, but the tumoricidal dose is generally far beyond the tolerance of surrounding structures.

Several observations indicate that hormones greatly influence the evolution of the tumor. In the first place truly neoplastic melanomas are uncommon before puberty; anomalously, such lesions may be trichotic, whereas hair-bearing melanotic lesions in adults rarely become malignant. Secondly, malignant melanoma has not been reported in castrated persons. Finally, periods of elevated hormone levels (adolescence and pregnancy) are accompanied by excitation of tumor growth, and patients in this group have a notoriously poor prognosis[53] that is probably not af-

fected by abortion. The mechanism involved, at least as far as pigment production is concerned, may be related to the experimental inhibition of in vitro melanogenesis by glutathione (a source of sulfhydryl groups) and the release of the inhibition by estrogen[54] or the melanocyte-stimulating hormone,[55] both of which are elevated during pregnancy. Therapeutic use of sulfhydryl compounds, however, might prove of little value, because, as mentioned above, agents that depigment the tumor do not necessarily slow its growth.

In the past, some investigators doubted the existence of the melanocyte-stimulating hormone as a separate pituitary secretion in man.[56] More recent work has shown that many of the earlier experimental results were due to the contamination of commercial ACTH with intermedin[12]; consequently, melanocyte-stimulating properties were ascribed to the former compound. There is at least one theoretical reason why ACTH and cortisone should result in melanization — namely their ability to depress blood glutathione (a source of sulfhydryl) levels.[57] In some unexplained fashion epinephrine blocks the melanophore-stimulating effect of the melanocyte-stimulating hormone, and ergotamine abolishes this blocking action.[12] Large-scale trials of sympathomimetic agents in malignant melanoma have not been reported. The effect of the adrenal cortex on melanocyte development and melanogenesis is undoubtedly complex, but, in tissue cultures of embryonic chick skin, desoxycorticosterone acetate inhibits melanocyte development.[58] There is evidence that junctional nevi have occurred in association with ACTH or cortisone therapy[59] although, again, with ACTH, contaminating melanocyte hormone may have been responsible. Lorincz[13] discusses the possibilities of a mechanism of action of melanocyte-stimulating hormone and the hormonal interrelations.

To eliminate melanocyte-stimulating hormone, surgical[60] and irradiation[61] hypophysectomy have been performed, with variable results on tumor growth. Bilateral adrenalectomy[53] and castration are without definite beneficial effect on spread of the tumor. Castration protects against the induction of a malignant melanoma, but once neoplasia has occurred the malignant process does not appear to be hormone dependent.

Specific chemotherapy against melanotic tumors is not yet available. Experimentally, the folic-acid antagonists[62] have failed to cause dissolution of the tumor. Radiomimetic agents such as the nitrogen mustards show little activity against these growths,[63] perhaps owing to the fact that a malignant melanoma is generally more radioresistant than its environment. Experimental inhibition of melanotic tumors by viral agents has been briefly reported.[64]

I^{131}-labeled gamma globulin prepared against concentrated melanin particles has been found not to carry the isotopes to the tumor site, and it has been suggested that the macromolecule antibody was unable to penetrate the walls of the malignant cells.[65] Neither tracer nor therapeutic doses of I^{131} are taken up by human melanomas in vivo,[66] and there is no demonstrable affinity of the tumor for radioactive phosphorus or copper.[9] Kennedy et al.[67] found, however, an increased uptake of P^{32} in ocular "melanosarcomas." Marcus and Rotblat[68] observed no uptake of I^{131} diiodotyrosine in malignant melanomas. From purely theoretical considerations this compound would be expected to have no activity, since Cushing[69] clearly defined the structural requirements necessary for a compound to be acted upon by tyrosinase. Agents substituted adjacent to the reactive phenolic hydroxyl group were entirely lacking in ability to act as substrates. The use of chelating agents in an attempt to bind the copper of tyrosinase has not been reported.

Although inhibition of melanin formation does not necessarily result in tumor necrosis, cells in the pigmented tumor that concentrated the radioactive antimetabolite would be selectively irradiated if suitable antagonists of tyrosine (metabolic analogues) were discovered and made radioactive. Tyrosine itself faces numerous metabolic pathways; hence, later products in the chain of conversion (tyrosine ⟶ melanin) would have to be employed to avoid competition with other tyrosine-utilizing systems. Screening of potential antagonists can be carried out in the laboratory by means of tissue-culture growth,[70] microbiologic assay,[71] manometric determinations[72] and in vitro colorimetric studies of melanin production.[73] Promising compounds may then be tried in vivo against animal melanotic tumors such as the Harding–Passey mouse melanoma.

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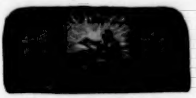

THE USE OF BLOOD IN MASSACHUSETTS HOSPITALS

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THE demand for human blood for therapeutic purposes in Massachusetts has nearly trebled during the past seven years, as indicated by the data reported below.

In 1947 Moore, Edsall and Getting[1] described the use of blood before the inception of the present cooperative effort by the hospitals and the American Red Cross to supply blood needs within the Commonwealth. To a survey questionnaire 94 Massachusetts hospitals replied in 1944, and 78 in 1947. This survey showed the 1947 use of blood to be 3.4 pints per hospital bed per year (an estimated total of 40,000 pints). Through the combined efforts of the Massachusetts Medical Society Supervisory Committee on Blood Banks, the Red Cross Regional Blood Center and all Massachusetts hospitals using blood, accurate figures of the current situation have been compiled. This accuracy is evidenced by the fact that of 76,971 pints sent to hospitals by the Red Cross during the twelve months ending June 30, 1954, nearly all, or 76,072, were reported as received by the hospitals.‡ For this period blood was used at the rate of 7 pints per occupied bed, or 6.7 pints per total bed. These figures, as in the 1947 report cited above, represent use in short-term hospitals only.

At a national level it is estimated that in the twelve months from July, 1953, to June, 1954, 3,807,000 pints of blood were used in 3547 hospitals throughout the United States. This covers almost all the hospitals in the country with any appreciable blood use. Of this amount the blood program of the American National Red Cross[2] supplied 1,522,970 pints, or 40 per cent of the total. The percentage in any area supplied through the Red Cross varies widely. In many areas there is no Red Cross blood program, and all blood is supplied by hospitals or community blood banks. In other areas — for example, Connecticut, Vermont and New Hampshire — the Red Cross supplies almost the total needs. In Connecticut the proportion supplied by the Red Cross is about 90 per cent, and 10 per cent is collected by hospital blood banks. In Massachusetts the Red Cross supplies half the blood, and the hospital blood banks supply the other half.

The 5077 pints of Red Cross collected blood listed in Table 1 as returned to that organization were processed by drawing off the plasma and sending it to the Massachusetts Institute of Laboratories for the production of albumin and gamma globulin. This laboratory is one of several under contract to process outdated blood from the civilian program of the Red Cross. The limited supply of albumin available at the Red Cross Center for distribution without cost to hospitals and physicians constitutes Massachusetts' share of this national plasma salvage program. The remaining 14,608 pints disposed of by the hospitals were in part utilized by hospitals to prepare plasma for their own use and in part sent directly to the laboratories mentioned above for further production of albumin. The State Laboratories and the hospital blood banks have a program, separate from the Red Cross plasma salvage program, established by the Massachusetts Medical Society committee, for processing blood drawn by hospitals into albumin and returning this product to hospitals in proportion to the amount of plasma they have sent.§ Outdating of blood in Massachusetts for the period studied was 13.2 per cent — a figure that compares favorably with national averages.

The supply of blood by the Massachusetts Red Cross blood program within the State varies much as it does nationally. During the year studied whole or partial blood needs were supplied to 176 hospitals. Of this number 60 received their total supply from the Red Cross, and the remaining 116 an average of slightly less than 50 per cent, ranging from 30 to 90 per cent. In the twelve months from July, 1953, through June, 1954, hospitals reported that they drew 71,573 pints in their own blood banks and that the Red Cross furnished them with 76,072 pints of bottled blood. For the blood drawn in hospitals 7124 donors were recruited by Red Cross chapters. It is obvious that the contributions of the 116 hospitals that bled donors helped the Red Cross fully to supply the 60 hospitals that did little or no bleeding of donors. The present level of financial and blood-donor support of the blood program does not permit collection of much more than 83,000 pints of blood yearly by the Red Cross. In any event a completely centralized blood service is not considered desirable, even if attainable, in view of the necessities of civil defense and the specific needs of hospitals for freshly drawn blood, plasma or platelets.

It is of considerable interest in hospital planning to know how many pints of blood are needed per year per occupied bed in the various classes of hospitals.

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‡Complete figures for January through December, 1954, show a total usage of 153,699 pints; 80,784 came from hospital blood banks, and 71,935 from the Red Cross; 12 per cent were outdated.

§Dr. Johannes Ipsen, director of the Massachusetts Institute of Laboratories, estimates that somewhat more than half this amount is received at the Laboratories.

In Table 2 the occupied hospital beds are grouped as in the June, 1954, issue of *Hospital* magazine, and the data given are based on the official number of beds listed in that publication. The great difference in usage between long-term and short-term hospitals is evident. Long-term hospitals in the Commonwealth are for the most part mental hospitals or those for the chronic care of organic disease.

To compare the use of blood as reported by Moore et al.[1] with the current amounts given in Figure 1 comparative data based on total hospital beds and on occupied beds are included.

Every year a certain quantity of blood is exchanged between hospitals. In the first six months of 1954 a total of 4939 pints was reported as having been transferred to other hospitals and 3275 pints as received in a similar manner. This discrepancy indicates a tendency on the part of hospitals to report more fully on outgoing than on incoming blood.

TABLE 1. *Blood Available to and Disposition by Hospitals, July, 1953, through June, 1954.*

ITEM		PINTS	PERCENTAGE
From Red Cross Center		76,971	52.0
Drawn by hospitals		71,573	48.0
Total available to hospitals		148,544	100.0
Transfused in hospitals		128,859	
Remainder (presumably outdated)		19,685	13.2*
Returned to Red Cross	5,077		
Otherwise disposed of by hospitals	14,608		

*Percentage of total available.

That the use of blood by hospitals for short-term care is quantitatively the most important is brought out by the fact that in 60 hospitals receiving their total supply from Red Cross and collecting none themselves, 5300 pints of blood were supplied in the twelve months studied, of which 4682 pints went to supply 1092 occupied beds in short-term and 618 pints

TABLE 2. *Use of Blood in Relation to Occupied Beds, July, 1953, through June, 1954.*

ITEM	NO. OF HOSPITALS	OCCUPIED BEDS	PINTS USED	AVERAGE PINTS/OCCUPIED BED/YR.
All short-term hospitals	142	17,497	123,669	7.0
All long-term hospitals	76	25,653	5,233	0.20
Teaching hospitals in Greater Boston	9	4,262	42,861	10.0
Obstetric hospital in Boston	1	147	435	3.0
Nonteaching hospitals outside Boston	9	1,271	10,354	8.0

to 24,373 occupied beds in long-term hospitals. Thus, there is a slight use by nonmental hospitals for long-term care, chiefly tuberculosis sanatoriums, and a very small use by mental hospitals in relation to their large bed capacity (Table 3).

All the short-term hospitals that collect none of their own blood are small in bed capacity and in the use of blood in relation to bed capacity. In a second group of short-term hospitals that collect some (less than 10 per cent) of their total supply, a few hospitals with large bed capacity that use over 1000 pints yearly

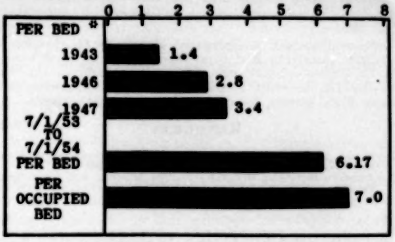

FIGURE 1. *Pints of Blood per Hospital Bed per Year. *Data from Moore et al.[1] (All data are from short-term hospitals.)*

rely on the Red Cross to supply 90 per cent of their needs.

DISCUSSION

In the interpretation of data pertaining to the operation of a blood program a distinction should be preserved between blood demand and blood supply. The magnitude of the potential demand for blood is

TABLE 3. *Blood Supplied by the Red Cross to Hospitals Not Collecting Any Blood (July, 1953, through June, 1954).*

TYPE	NO. OF HOSPITALS	NO. OF OCCUPIED BEDS	NO. OF PINTS SUPPLIED	NO. OF PINTS/OCCUPIED BED/YR.
Short term	38	1,092	4,682	4.28
Long term:				
Chronic & tuberculosis	9	2,149	279	0.12
Mental	13	22,224	339	0.015

unknown. Practically, the problems of collection, processing and distribution are related to the effective demand, as measured by the quantity used in hospitals and that on hand, as well as the portion of the collected total that is destined for use as plasma or plasma fractions. Since the use of whole blood in short-term hospitals represents the bulk of the tangible demand and since the facilities for its administration are unequally distributed geographically, even within small areas, the actual hospital consumption in a specified city or town can be appreciably smaller or larger than the supply obtained from voluntary donors therein. The Red Cross blood program has been helpful in smoothing out this inequality, which also stems in part from migration of ill or injured residents of rural and suburban communities to city hospitals.

Summary

Statistics based on nearly complete reports are given, showing the use of blood in Massachusetts hospitals in 1953-1954. The average number of pints needed per occupied bed per year according to the type of hospital is given for its value in hospital planning. The necessity for co-operative efforts between hospital blood banks and the Red Cross blood program, to meet total needs, is emphasized.

We are indebted to George W. Hervey, Sc.D., director of statistics, American Red Cross Blood Program, Washington, D. C., for his valuable suggestions and criticism and to Miss Phyllis Lovell, chief statistical clerk, Massachusetts Red Cross Blood Center, for compilation of hospital reports.

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DOCTORS AFIELD

John Richardson

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It is difficult for the casual reader to decide whether John Richardson should be considered first and foremost a physician or a naturalist. Chronologically, he was first a physician. On the basis of his writings and posthumous fame, he was first a naturalist. It was in the combined capacity of physician and naturalist that he went farthest afield, geographically speaking at least, as an Arctic explorer.

Richardson was born in Dumfries, Scotland, in 1787. His father was chief magistrate and justice of the peace, and a friend of the town's most famous citizen, Robert Burns. Between bouts of congestive heart failure, the poet was a regular visitor to the Richardson household, and his warm personal charm soon captivated young John, as it did all children. When at the age of seven he borrowed Burns's copy of the *Faerie Queen* it proved to be a harbinger of a lifelong love of poetry.

Richardson's medical education began at the age of thirteen, when he was apprenticed to a surgeon. At twenty he was gazetted assistant surgeon in the Royal Navy. This was a humble position, since the surgeon's mate was regarded as little more than a civilian afloat, with the slightest possible trace of medical knowledge. But Richardson enjoyed life at sea, and he advanced rapidly in grade. For a time he was on duty in the Atlantic, taking part in the raids on the Georgia coast with Cockburn. He wrote home deploring the useless destruction of property in America, especially "the few works of art which were found there."

After Waterloo he was permitted to complete his medical training. He received the medical degree from Edinburgh in 1817 for a thesis on yellow fever. While there his lifelong interest in the natural sciences was awakened. The recognition of his ability both as a physician and as a naturalist, together with his naval record, was responsible for an invitation from John Franklin to join his forthcoming expedition to the Canadian Arctic.

With Richardson as second in command, the expedition traveled over 5500 miles in spite of extreme hardship. The supply system failed, and the entire party almost starved. Richardson himself had to execute an Indian who had turned cannibal. Somehow,

Sir John Richardson (Reproduced from Mellraith, J. Life of Sir John Richardson. London: Longmans, Green, 1868).

many specimens of the flora and fauna were returned to England in 1822, and he spent the next few years studying and classifying them.

A second Franklin expedition in 1825 was uneventful, though successful, and Richardson returned to be physician at the new naval hospital at Chatham. There he began his monumental work, *Fauna Borealis-Americana*. This was a complete and detailed study of the quadrupeds, fishes, birds and insects of northern Canada, with Richardson as editor and chief contributor. The first of the four volumes was published in 1829.

At fifty-one he was appointed physician to the famous Royal Naval Hospital at Haslar, near Plymouth. Haslar, still in operation today, was at that time the largest hospital in Europe. It was constructed at a phenomenal cost of £100,000, covered 30 acres and housed 2200 patients. Even in Richardson's day it had a noble tradition, the first physician-in-chief

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having been James Lind, author of the *Treatise on Scurvy*.

At Haslar Richardson made some of his few significant medical contributions, which were chiefly organizational. He was horrified at the treatment of the insane. By demonstrating to the Admiralty that humane methods were more efficient, and especially more economical, he obtained the privilege of introducing reforms. Their greatest importance lies in the fact that they were later adopted in all naval installations. He also visited the famous nursing institute of Pastor Fleidner at Dusseldorf, with the purpose of improving nursing in naval institutions.

Though devoted to his medical career, Richardson found time for the study of the natural sciences. He was recognized as an authority in the field by having pupils of his own. The most famous of these was Thomas Henry Huxley, who later dedicated an important work to his teacher, inscribed "To the Founder of my Fortunes."

At fifty-three Richardson was appointed inspector of hospitals for the Navy. In 1846 he was knighted for his part in the Arctic explorations and for his contributions as a naturalist. At sixty-one he was selected to lead one of the search expeditions for his friend, now Sir John Franklin, lost in the Arctic. Despite his years, no one doubted his fitness, and the unsuccessful search was accomplished with characteristic thoroughness and efficiency.

Passed over because of his age in the selection of chief inspector of hospitals, Richardson retired in 1855, but he did not cease to study or to write. During his remaining years he traveled widely, published several papers on zoology and botany, and contributed to the *Encyclopedia Britannica*. He also contributed to the Philological Society's dictionary and made a complete study of the works of his childhood friend, Burns. In 1865, at the age of seventy-eight, he died suddenly of what was probably a coronary occlusion.

Richardson was a quiet, austere man. His reserve was seldom penetrated, though Huxley said of him, "in truth, he was one of the kindest-hearted and gentlest of men." He demanded the same long hours at work and the same careful and precise observations from his subordinates that he demanded from himself.

Devoted to his family, he was in turn adored by them, especially by his children. His many letters reveal a tender regard for his family and a deep and solacing religious faith. In the choice of his three wives, he was apparently most fortunate, if for no other reason than that the given name of each was Mary.

Richardson's journals of his Arctic travels are models of accurate, complete and well written scientific reporting. They illustrate his broad scientific interests, for they include not only observations on flora and fauna but also important geologic information, elaborate ethnologic data and records of solar radiation, climatic conditions and soil analysis.

Sir John Richardson was a physician of whom the medical profession should be proud. His early medical training in observation must have been an important contributing factor to his success in the several fields in which he was eminent.

I am indebted to Miss Dorothy Long, reference librarian, and to the staff of the Medical Library of the University of North Carolina for assistance in locating and obtaining source material.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41271

PRESENTATION OF CASE

First admission. A twenty-eight-year-old shipping clerk entered the hospital because of easy fatigability.

Four years before admission he had a cold and "bronchitis." At that time he became easily fatigued and lost his appetite. His weight fell from 250 to 185 pounds within six months. The fatigability and anorexia persisted, but his weight remained at 180 to 190 pounds over the next three and a half years. Four months before admission he consulted a physician because of a sore throat. A red-cell count at that time was 3,500,000. He was given a series of liver injections with some improvement, but with cessation of therapy the red-cell count again became 3,500,000.

The family history was remarkable only in that most members of his family were tall and lanky.

Physical examination revealed an apathetic, well developed, well nourished man in no distress. His height was 191.5 cm., his arm span 192 cm., and his weight 180 pounds. The only abnormal findings were absent knee and ankle jerks and abdominal reflexes. Hair distribution was normal. The testes and prostate were normal.

The temperature was 97.6°F., the pulse 90, and the respirations 22. The blood pressure was 115 systolic, 75 diastolic.

The urine had a specific gravity of 1.022 and was normal. Examination of the blood revealed a hemoglobin of 74 per cent, a red-cell count of 3,800,000 and a white-cell count of 7600, with 54 per cent neutrophils, 33 per cent lymphocytes and 7 per cent eosinophils. A blood Hinton test was negative. The urinary 17-ketosteroid excretion varied from 2.7 to 3.9 mg. in three twenty-four-hour specimens (normal, 8-20 mg.). An x-ray film of the chest was normal.

The patient was treated supportively and discharged on a high-protein diet.

Second admission (three years later). He was readmitted for a checkup. He stated that he felt very much better than during the previous admission.

Physical examination revealed a weight of 161 pounds. The teeth were carious. Knee and ankle jerks were now active. Visual fields were normal except for a cataract in the right eye.

The temperature was 98.4°F., the pulse 100, and the respirations 20. The blood pressure was 100 systolic, 60 diastolic.

The urine had a specific gravity of 1.014 and gave a ++ test for albumin; the sediment contained 3 white cells per high-power field. Examination of the blood showed a hemoglobin of 10.1 gm. per 100 cc., a red-cell count of 3,390,000 and a white-cell count of 10,600, with 74 per cent neutrophils, 19 per cent lymphocytes and 7 per cent monocytes. The red cells appeared normal on smear. A reticulocyte count was 0.4 per cent. The sugar was 86 mg., the nonprotein nitrogen 25 mg., and the total protein 5.2 gm. per 100 cc. The cholesterol was "normal." The 17-ketosteroid urinary excretion was 2.1 and 3.6 mg. per twenty-four hours; the FSH (follicle-stimulating hormone) was positive for 6.5 mouse units in twenty-four hours. The spinal-fluid protein was 69 mg. per 100 cc., and the spinal-fluid Wassermann test negative. X-ray films of the chest and a gastrointestinal series were normal, and barium-enema examination was negative. Skull films demonstrated the sella turcica to be at the upper limits of normal in size, but the clinoid processes showed no erosion or decalcification. The facial bones did not suggest acromegaly. The basal metabolic rate was −30, −50 and −25 per cent on three occasions.

After the extraction of twenty-nine teeth, the patient lapsed into coma; the blood pressure was 85 systolic, 65 diastolic, and the blood sugar was 32 mg. per 100 cc. The coma responded rapidly to intravenous glucose. Aside from the dental surgery, therapy was supportive.

Third admission (three months later). The patient was readmitted for further study, although he had been feeling better and was working. Physical examination was not significantly different from that on the previous admissions. The spinal-fluid protein was 53 mg. per 100 cc. Stool examinations for ova and parasites were repeatedly negative. Free acid was present in the gastric juice. The serum sodium was 122 milliequiv. per liter, and the cholesterol 179 mg., the calcium 8.4 mg., and the phosphorus 3.3 mg. per 100 cc. A Wilder test showed 180.3 mg. of chloride per 100 cc. in the four-hour specimen (normal, 23 to 137 mg. — in Addison's disease 229 to 356 mg.) and 100.5 mg. in the twenty-four-hour specimen (normal, 48 to 125 mg. — in Addison's disease 139 to 352 mg.). An insulin tolerance test revealed a fasting blood sugar of 61.3 mg.; twenty minutes after insulin injection 51 mg., forty-five minutes 63 mg., sixty minutes 52.9 mg., ninety minutes 21.8 mg. and 120 minutes 52.9 mg. per 100 cc. FSH was positive for 6.5 mouse units but negative for 26 mouse units per twenty-four hours, and the 17-ketosteroids were

2.9 and 3.9 mg. per twenty-four hours. Liver extract was administered but was discontinued after testosterone propionate, 25 mg. a day, was begun, and he was discharged.

Fourth admission (three months later for study). Three weeks after discharge, the basal metabolic rate was −29 per cent and thyroid extract (0.09 gm. daily) was started. Two and a half months later two testosterone pellets were implanted. He had been doing physical work in the interim, had a better appetite and now weighed 173 pounds. In the hospital the hemoglobin was 10.1 gm., and the basal metabolic rate −42 per cent. Four 75-mg. pellets of testosterone were inserted subcutaneously.

Fifth admission (one year later), for severe rectal bleeding. In the interval since the last admission thyroid extract had been increased to 0.13 gm., then to 0.26 gm. daily; testosterone had been continued, and ferrosulfate and liver extract had been started. The physical examination was unchanged. The weight was 151 pounds. The hemoglobin was 8.8 gm. per 100 cc. Urine corticosteroid excretion was 0.16 mg. per twenty-four hours. The serum cholesterol was 146 mg., the total protein 5.32 gm., the albumin 4.05 gm., the globulin 1.27 gm., and the nonprotein nitrogen 35 mg. per 100 cc.; the potassium was 3.9 milliequiv., and the sodium 137 milliequiv. per liter. The basal metabolic rate shortly before admission was −35 per cent. After an incision and drainage of a rectal abscess the patient became hypotensive and somnolent. Ten per cent dextrose in saline solution, adrenocortical extract, testosterone propionate and 500 cc. of whole blood were administered, with improvement. An electrocardiogram five days postoperatively showed rather small QRS complexes in the limb leads and rather low T waves. A testicular biopsy showed hypospermatogenesis and absence of Leydig cells. Potassium chloride was started (1 gm. four times a day), and 3 DOCA pellets (75 mg.) were implanted subcutaneously. The patient was discharged to continue on thyroid extract, testosterone and DOCA pellets, ferrosulfate and a high-salt intake.

Sixth admission (two years later). He had been seen frequently as an outpatient in the interim, and the therapeutic regimen begun on the last admission had been maintained. There had been one episode of unconsciousness thought to be hypoglycemic in origin. At the time of admission the patient had gained 50 pounds and felt better than ever. Physical examination was as before, except for a slightly higher blood pressure of 122 systolic, 80 diastolic. Examination of the blood revealed a white-cell count of 6100, with 39 per cent neutrophils, 54 per cent lymphocytes, 1 per cent monocytes and 6 per cent eosinophils, and a hemoglobin of 10.7 gm. per 100 cc. The sodium was 140.6 milliequiv., and the potassium 4.9 milliequiv. per liter, and the total protein 6.13 gm. per 100 cc., with an albumin-globulin ratio of 2.08; the nonprotein nitrogen was 20 mg., the cholesterol 229 mg., and the protein-bound iodine 2.2 gamma per 100 cc. Urinalysis was negative. Twenty-four-hour urinary excretion of creatinine was 1.04 gm. Urinary FSH was negative for 6.5 and 13 mouse units per twenty-four hours; 11-oxysteroids were 0.08 mg. per twenty-four hours. Cortin assay was positive for 3 and negative for 24 mouse units per twenty-four hours. X-ray films of the skull demonstrated no change in the size of the pituitary fossa. An electroencephalogram was abnormal, showing "short, mild paroxysmal runs, which are symmetrical." Another testicular biopsy revealed findings similar to the previous ones except that a few small Leydig cells were present. After this biopsy the patient became severely depressed and had delusions and feelings of unreality. The depression lifted, and he was finally discharged.

Seventh admission (two years later for endocrine studies). In the interim he adhered to the therapy previously prescribed; DOCA was last given on the previous admission (225 mg. subcutaneously). In spite of a good appetite, he had lost 22 pounds since the previous admission. Two months before entry he had a gastrointestinal upset, and the daily dose of thyroid was reduced to half. The physical examination was as before. Visual fields were normal although there were poor convergence, premature arcus senilis and fine, dustlike lens opacities. The blood pressure was 90 systolic, 50 diastolic. The hemoglobin was 11.0 gm. per 100 cc., the eosinophils 217 per cubic millimeter, and the cholesterol 207 mg., the calcium 9.1 mg., the phosphorus 4.6 mg., and the alkaline phosphatase 5.0 units per 100 cc. The basal metabolic rate was −36 per cent. After 0.3 cc. of 1:1000 epinephrine the eosinophils fell from 120 to 84 per cubic millimeter in four hours. The Wilder test revealed a urinary sodium of 116.4 milliequiv. and a chloride of 93 milliequiv. per liter (normal, up to 40 milliequiv. per liter). The blood value of the sodium before the test had been 138 milliequiv., that of the chloride 106 milliequiv., and that of the carbon dioxide 29.3 milliequiv. per liter. A glucose tolerance test (0.8 gm. of glucose per kilogram of body weight) showed a fasting blood sugar of 81 mg.; at thirty minutes after glucose, of 104 mg.; at sixty minutes, of 106 mg.; at ninety minutes, of 112 mg.; at one hundred and twenty minutes, of 107 mg.; at one hundred and fifty minutes, 100 mg.; and at two hundred and seventy minutes 81 mg. per 100 cc. An insulin tolerance test with 4 units of insulin (0.05 units per kilogram of ideal weight) revealed 69 mg. of sugar before injection, 44 mg. twenty minutes, 32 mg. thirty minutes, 34 mg. forty-five minutes, and 48 mg. per 100 cc. sixty minutes after injection. The patient became weak and confused so that the test was terminated, and he was given orange juice. The 17-ketosteroid excretion was 0.8 mg. per twenty-four hours, the 11-oxysteroids 0.10 mg. per twenty-four hours, and the FSH negative for 6.5 and 13 mouse units per twenty-four hours. Starting on the fifteenth hospital day TSH (thyroid-stimulating hormone) was administered intramuscularly daily for six days. During and immediately after this course of TSH the basal metabolic rate rose to an average of −13 per cent. On the fifth day of the test

the protein-bound iodine was 4.6 gamma per 100 cc. During the month thereafter it varied from 3.3 to 5.7 gamma per 100 cc. The patient was discharged on a high-calorie diet, methyl testosterone linguets (30 mg. a day) and thyroid extract (390 mg. a day).

Eighth admission (two weeks later for study of basal metabolic rate). The hemoglobin was 9.5 gm. per 100 cc., the reticulocyte count 1.6 per cent, and the serum cholesterol 177 mg., and the sodium 139 milliequiv. per liter; the fasting blood sugar was 97 mg., the calcium 9.0 mg., and the phosphorus 4.9 mg. per 100 cc. The basal metabolic rate was −6 and −15 per cent. Two DOCA pellets were inserted in the left thigh, and he was discharged to continue the thyroid, methyl testosterone, iron and high-salt diet.

Final admission (four years later because of bizarre behavior). The patient had been placed on cortisone a year previously. He had been hyperactive during the week before admission; it was believed that some of this behavior was caused by the erratic intake of cortisone although he was also depressed over the severe illness of an uncle with whom he lived. Physical examination was unchanged. He weighed 185 pounds. The urine was normal. The hemoglobin was 15 gm., and the fasting blood sugar 77 mg. per 100 cc. Three electroencephalograms were symmetrically and diffusely abnormal. He was treated supportively, and after the implantation of more testosterone in the thigh he was discharged to be followed by his physician for control of testosterone and cortisone medication.

Over the next eight months he was seen by a psychiatrist in the Out Patient Department for various mood disturbances; thereafter he was not seen in this hospital. At the age of forty-two he died in a state mental hospital, twenty-two months after the last admission to the Out Patient Department.

Differential Diagnosis

Dr. George W. Thorn*: I am always delighted to discuss one of these cases in this amphitheater. The patient's height of 191.5 cm. (6 feet, 4 inches) paralleled the length of his history; I believe this is the longest protocol that I have ever had presented to me; to be sure, it covers a period of approximately eighteen years.

If one is presented with a young person who lives for eighteen years after the onset of a serious illness and who has a low ketosteroid of 2.1 to 3.9 mg. per twenty-four hours, the logical conclusion should be that he has a pituitary deficiency. The reason I can make this diagnosis immediately is the fact that the only other situation that can produce such a low total 17-ketosteroid level is primary adrenocortical deficiency in conjunction with primary testicular deficiency. Almost invariably patients with long-standing primary adrenal deficiency exhibit progressive disability. This is particularly true in cases of Addison's disease not due to tuberculosis of the adrenal glands.

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Summarizing briefly the clinical course of this patient, it can be stated that over a period of eighteen years he had lost 20 or 30 pounds of weight, and then with "supportive treatment" regained part of the weight loss and felt better. It is interesting that even when he felt better, between the ages of twenty-eight and thirty-one, he had a further weight loss of 20 pounds — in other words he decreased from a weight of 180 pounds to 160 pounds. At a weight of 150 or 160 pounds this tall man must have appeared to be very thin. The critical episodes in the illness occurred in conjunction with surgery: after a large number of teeth were extracted and after a rectal operation the patient went into a serious shock.

My problem, then, is to try to pick out the aspects of this history that are unusual and in a way set it apart from the ordinary history of pituitary deficiency, with which the majority of the findings are consistent. We see a number of patients at the Peter Bent Brigham Hospital whom Dr. Harvey Cushing operated on for pituitary tumors many years ago who are still remarkably well, despite very little demonstrable pituitary function. This case in that respect is consistent with those cases. The first thing I should like to take up is the initial examination, which was not remarkable except for the absence of knee and ankle jerks and abdominal reflexes. The hair distribution was normal. The ketosteroid excretion was 2.7 to 3.9 mg.; this almost certainly means either that the testes were abnormal or that the prostate was small. If one or the other was not small, that would seriously suggest that this change had occurred in a very short time. In a young large male with such a low ketosteroid level we have to assume the loss of both adrenal and testicular functioning tissues, which are the sources of urinary ketosteroid.

Throughout this whole story there was anemia, which is consistent with pituitary insufficiency. What is there in pituitary insufficiency that causes anemia? Two factors that are known today are the thyroid-adrenal effect on bone marrow and perhaps also growth hormone or a pituitary factor closely related to it, which may be hematopoietic. There is a great deal of evidence to suggest this. Animal experimental work carried out by the group in Berkeley[1] has actually demonstrated that a fraction of the anterior pituitary gland is strongly hematopoietic. Our experience has been that in a patient with multiglandular deficiency, anemia is always a prominent characteristic. Only since cortisone replacement in addition to thyroid replacement has been possible has the anemia improved significantly. The anemia in pituitary insufficiency in general is greater than that in primary adrenal insufficiency. The protocol does not tell us when this person was first started on cortisone, but I shall assume that the improvement in the hemoglobin values late in the course was due largely to the supplementary hormonal therapy of cortisone, testicular hormone and thyroid. It would be interesting and unusual if without cortisone therapy this patient's anemia had been restored to normal.

A PHYSICIAN: Cortisone therapy was started four and a half years before death.

DR. THORN: Patients who had Addison's disease for years, when treated with desoxycorticosterone alone, showed persistent anemia. When cortisone became available, the anemia of these patients was corrected.

The second interesting point is the testicular function. If I can rely on the 17-ketosteroid determination, which was confirmed over and over again, I can say that the patient had gonadal insufficiency. Did any biopsy show actual derangement or loss of both Leydig cells and seminiferous tubules in the testes? At the same time that the ketosteroids were low the FSH was positive. One would therefore have to postulate that initially the patient had a primary gonadal injury or deficit. Later in the course the FSH values became negative and pituitary gonadotrophic deficiency could be suspected. A negative FSH value is not really as significant as a positive value. A positive value in a male is strong evidence against total pituitary failure so this patient had some pituitary function when he was first admitted to the hospital.

The third interesting factor is the neurologic and psychologic disturbances. There were absent knee jerks and abdominal reflexes. Spinal-fluid examinations were frequently made, which is interesting, for ordinarily this procedure would not be carried out in a gonadal deficiency alone. Then, there was a severe mental depression, a psychotic reaction, after the second testicular biopsy, and the implication that the last years of therapy were complicated by marked mental disturbances of the patient. What does this mean? Does it mean that I have to deal with a specific neurologic or psychologic condition besides specific hormonal deficiency? Patients with pituitary insufficiency may present themselves with convulsive seizures or with symptoms that are suggestive of hypoglycemic episodes, but the more we study these patients, the more we are convinced that there are two groups of hormonal disturbances with bizarre psychologic reactions: one occurs in patients with Addison's disease, and the other in patients with Cushing's syndrome. Anyone who has followed a group of patients with Cushing's syndrome is impressed with the number and seriousness of the psychologic reactions. Much of the difficulty in taking care of such patients clinically is related to the psychologic disturbances. I assume that this patient, although he got along fairly well, had never felt quite right, that he had, in addition, a profound hormonal deficiency of both adrenal cortex and gonads and that he had all the changes in brain metabolism present with adrenal insufficiency. The cerebral changes were demonstrated characteristically in the slowed electroencephalogram. As time went on he had complicating reactions. Many of these patients do have severe psychotic reactions. We lost a patient with Addison's disease in the days before cortisone because he steadily refused to eat. We lost another patient on cortisone because he had a psychologic reaction and stopped taking the cortisone. The patient on cortisone who suddenly stops hormone therapy is in a very vulnerable position. We see many psychologic reactions in patients with adrenal deficiency, either primary or secondary, when they are first started on cortisone. In fact this is the only known risk, aside from tuberculosis, that one has to face in starting moderate doses of cortisone in substitution therapy. Many patients have experienced more than euphoria on their initial doses of cortisone, and many have become frankly psychotic. I think these psychologic changes were the background for more serious difficulty when the testicular biopsy was carried out. It would be interesting to know whether he tolerated the cortisone therapy well when it was initiated or had more psychologic reaction to it than one would anticipate ordinarily.

In the terminal event one is up against a very difficult situation because the patient was psychologically disturbed whether he was receiving cortisone or not. Since we rely on oral medication these days, this is a difficult situation. With thyroid the situation is simpler, for if the patient does not take thyroid for a week or two, it is not too serious, since the clinical condition deteriorates very slowly. If the patient does not take the cortisone for a day or two, he may die. This patient, who could get along safely over the years with no substitution therapy in a lowered metabolic state, could not tolerate for forty-eight hours the withdrawal of cortisone once he had been maintained on it. It is easy to see why the final period of treatment became so complicated and most certainly involved a high degree of co-operation between the psychiatric group and the group interested in the hormonal manipulation. This is one situation in which pellet implantation of cortisone might have been seriously considered.

The alteration in glucose metabolism that runs through this protocol is of considerable interest to me. There is a strange story here. In this patient, who at the onset looked like a relatively simple case of panhypopituitarism, the first blood sugar examination was not low. If by chance the determination was in error or if some other mechanism were responsible subsequent determinations over the years should have revealed that. The second point of interest is that he did remarkably well over a long period, and the third is that there was not a single documented hypoglycemic episode except when major surgery was performed or insulin was given. The one probable instance of hypoglycemia occurred when the patient was given insulin intravenously — the dose was not stated. The sugar at the beginning and up to sixty minutes continued at low normal levels and then fell to 20 or 30 mg. That is not typical of uncomplicated hypopituitarism, for those patients, as Fraser, Albright and Smith[2] have shown, are extremely sensitive to insulin. After an oral glucose tolerance test with 0.8 gm. of glucose per kilogram of body weight the blood sugar curve was flat. The fact that he did not have a reactive hypoglycemia immediately makes me think either that he did not absorb the glucose readily —

that he did not have either severe adrenal insufficiency or hypopituitarism — or that he had a complication that modified the hypoglycemic response. The second insulin test did produce a real degree of hypoglycemia, but it was possible to carry out the test for sixty to ninety minutes, which is reasonably good, although the second test, if the same dose of insulin was used, showed a deterioration of this mechanism.

A PHYSICIAN: He had hypoglycemia before he had the test.

DR. THORN: Do you know whether the dose on the second test was the same?

A PHYSICIAN: We were unable to find the dosage.

DR. THORN: If the dose was the same there was progression of sensitivity to insulin over this period.

In trying to think this through, I came to the following conclusions. The patient lost weight, and had enough abnormality in carbohydrate metabolism to suggest an excess of growth hormone or a deficiency of insulin throughout the course of the illness. I assume that he had a masked diabetes mellitus or relative insulin deficiency in conjunction with anterior pituitary deficiency. I do not know whether it was possible to show this histologically in the pancreas; usually, the pathologist is unable to detect this degree of insulin deficiency without recourse to elaborate animal assay of the insulin content of the pancreas. My working diagnosis in caring for this patient would have been that he had an anti-insulin mechanism that prevented him from experiencing great changes in blood sugar.

How can these patients with apparently gross hormonal deficiencies get along so well? This patient, if he had pituitary insufficiency, also had thyroid and adrenal insufficiency, accompanying a very low metabolic rate. We know that the hormones in general add nothing new to the body in terms of metabolic processes. Actually, what they do is to increase the efficiency of the metabolic processes. When the metabolism is −40 per cent the amount of hormone needed is extremely small; therefore, it is possible for a person to maintain himself even with severe hormonal deficiencies over prolonged periods. There is a great body of evidence that with pituitary insufficiency all steroid production by the adrenal gland is not suppressed. It is entirely possible for an appreciable amount of salt-retaining hormone (aldosterone) to be found even in the presence of a small atrophic adrenal gland. Such a patient would not require much besides an adequate sodium chloride intake to maintain himself.

I should like to point out the difference between a patient with pituitary insufficiency and a patient with primary adrenocortical insufficiency. A patient with primary adrenocortical insufficiency has to meet the demands of a fairly normal thyroid function, fairly normal gonadal function and fairly normal over-all metabolic functions. Against the normal requirements of the other systems, the adrenal insufficiency is relatively more serious than that in a patient who is hypophysectomized and whose whole metabolism is reduced. That is clearly illustrated by the difference in therapy for a diabetic patient who has been adrenalectomized compared with one who has been hypophysectomized. Luft and the group in Stockholm[3] now have a large number of diabetic patients who have been hypophysectomized. It is easier to deal with the hypophysectomized diabetic patient than with the adrenalectomized diabetic patient. The insulin requirement is small, and the cortisone requirement is small.

Since this patient initially entered this hospital in 1940, it would be interesting to speculate how the treatment he would have received today would have differed from that available fourteen years ago. After a 17-ketosteroid value of 2 to 3 mg. was found in a young man, what should have been done? The first thing that I should do would be to take an x-ray film of the skull because the most likely cause of a low ketosteroid in a male not suffering from severe, prolonged chronic illness is both testicular and adrenal deficiency; the most likely cause of two peripheral-gland deficiencies is anterior pituitary insufficiency.

Today we are in a position to make definitive measurements and we do not have to rely on insulin tolerance tests, Keppler–Power water tests or Wilder tests of sodium depletion. For thyroid studies we can rely on a specific hormonal response — that is, change in basal metabolic rate, increased iodine uptake in the gland after TSH administration and an increase in protein-bound iodine in the blood. TSH was given to this patient; from the results one can assume that his thyroid gland could respond to TSH. The most definitive mechanism for measuring adrenal insufficiency is the ACTH test. It was notably lacking in this case. I cannot say at this moment whether it was done and was not reported or whether it was not done. Today this patient would certainly have had an ACTH test, with ketosteroid and 17-hydroxysteroid determinations in the urine.[4] This would settle the question of whether or not there was primary adrenocortical insufficiency. It would not tell us whether there was primary pituitary insufficiency. Ordinarily, we would not call an ACTH test positive unless we were able to carry it out with intravenous administration of ACTH. The screening test does not need to be done with intravenously administered ACTH, but certainly the definitive test should be because by that route the ACTH is most certain to reach the adrenal gland. If there were a primary adrenal deficiency and primary pituitary deficiency, one could not diagnose the deficiency of ACTH per se. We have no hormone — no preparation that I know of—that will with any reliability stimulate the pituitary gland. This patient had an epinephrine test, but we know now that there is no evidence that epinephrine increases the production of either ACTH or adrenocortical hormone. The eosinopenia from epinephrine can be entirely independent of the adrenal gland and can be additive to either ACTH or cortisone. With FSH determinations and testicular biopsy we have the opportunity to differentiate primary and secondary hypogonadism. The

only pituitary hormonal measurement that we cannot carry out is of growth hormone. There are no good practical methods of assay. Insulin assays are almost on the horizon, but at the present time it would not be practical to carry out an insulin assay on a patient like this.

What does the sella turcica in this patient indicate? This large man had a sella turcica at the upper limits of normal in size, which in eighteen years did not change. He had no visual disturbances other than those that could be accounted for by cataract. This would most likely indicate a stationary enlargement such as a cyst rather than a tumor.

I should like to discuss the slight elevation of the spinal-fluid protein. I wonder whether, if there was not a complicating neurologic abnormality, this modest elevation of spinal-fluid protein was consistent with the diagnosis of mild diabetes. Patients with diabetes mellitus characteristically have elevation of the serum and spinal-fluid protein. This patient's spinal-fluid protein was slightly above normal throughout the course and could have been consistent with metabolic effects of diabetes, which were masked in the periphery by the superimposed adrenal insufficiency.

I cannot eliminate, in a patient with this grade of hormonal deficiency, a primary disturbance of the nervous system, but it certainly was not a progressive disease over a period of years. There was a straightforward psychologic disturbance, which could certainly be explained by the hormone deficiency, the chronic disease and replacement therapy.

With the absence of an expanding sella turcica, one might suppose that this man in his growth to 6 feet, 4 inches, used up the pituitary gland to a large extent or perhaps he had a superimposed tumor. Statistically, I should vote for a small chromophobe adenoma, which compressed the pituitary gland, which gave him initially thyrotrophic and ACTH deficiency and which did not affect the gonadotrophic-hormone production. In addition he had primary disease of the testes and undoubtedly had insulin deficiency of a mild nature, which might have shown up in the pancreas but which again could only have been determined by insulin assay and careful metabolic studies of fat utilization and ketone-body formation. He had another finding that makes me think that he had a modicum of adrenocortical tissue. During part of the illness, he had free acid in the stomach. That, together with the maintenance of the blood sugar at a good level, suggests some function of adrenal cortex throughout part of his life. The amount of hormone that he needed, however, was very small. Whether or not at the end of eighteen years of pituitary deficiency he could have had superimposed primary adrenocortical deficiency I cannot say from the observations here. At this point that would be easily detected by the ACTH test. In a patient like this it would be necessary to give ACTH for several days because of the long-standing deficiency. To do this neatly our procedure would be to put this patient on fluorohydrocortisone, which is so powerful that the amount that one needs to give is 1 mg. a day, which would not give him any appreciable ketosteroid or 17-hydroxysteroid in the urine. On 1 mg. a day he would be protected from the toxic action of ACTH if he did not have any adrenal cortex to respond to ACTH. By that means I could decide whether he had primary or secondary adrenal insufficiency. The psychologic reaction, I think, was partly integral in this man and partly the result of the physiologic disturbance, particularly the adrenal hormone and androgen deficiencies and the effect of the long-continued, chronic illness. The testicular deficiency, I believe, was primary, but there was also pituitary deficiency of ACTH and TSH, and undoubtedly there was some insulin deficiency.

DR. BENJAMIN CASTLEMAN: Would you like to see the x-ray films of the skull?

DR. THORN: No; I think the report is acceptable. The films were taken over a long period and showed no enlargement of the sella turcica.

A PHYSICIAN: Do you have a comment on the high requirement of this man for thyroid at the age of thirty-nine?

DR. THORN: I am glad you asked about that. Part of my security in making a diagnosis of hypopituitarism rests on the resistance to *USP* thyroid therapy. In earlier days, when thyroid was the only hormone available, it was fairly generally admitted that there was not much point in giving it to the patient with hypopituitarism. Some patients show relative resistance to thyroid therapy perhaps because of the absence of growth hormone and the deficiency of cortisone. We have shown in 1 patient with a thyroid and adrenal-hormone deficiency that when we gave thyroid the electroencephalogram did not change appreciably; when we gave cortisone alone the electroencephalogram did not revert to normal appreciably, but when we gave thyroid and cortisone together the electroencephalogram was nearly normal. There is a belief that, when enough thyroid is given even to the patient with hypopituitarism, he may quickly show toxic manifestations of thyroid, but given a patient with hypopituitarism one can almost predict that there will be little or no effect from thyroid. It has certainly been my experience, and I think it is the experience in the literature, that the patient has a low basal metabolic rate but if he is given thyroid he shows very little change in the basal metabolic rate.

I should like to ask Dr. John B. Stanbury, if he is here, why with TSH there is such a striking change in the metabolism on a relatively short course. In part we used to believe that the TSH was toxic and that this was perhaps a nonspecific fever and so forth. I gather that this patient showed very nicely — and we have seen it in a patient with hypopituitarism — a relative refractoriness to thyroid and that he apparently stimulated his own gland and something happened to give him a unique change. Whether this can be reduplicated I do not know. It will be interesting to study the effect of compounds such as tri-iodothyramine in patients of this type. The release of a

small quantity of this hormone and the immediate response that it characteristically elicits might explain some of the changes observed after TSH administration.

DR. CASTLEMAN: Dr. Stanbury is in Holland.

DR. FARAHE MALOOF: I wonder if you have seen patients with real hypopituitarism who were able to tolerate this much thyroid, 6 gr. (1.8 gm.).

DR. THORN: He had over 6 gr. Do you know what the preparation was?

A PHYSICIAN: Burroughs-Wellcome.

DR. THORN: I thought Burroughs-Wellcome thyroid was standardized on the English pharmacopoeia.

DR. MALOOF: No; it is not; it is *USP*.

DR. THORN: Usually, when I have been told the dosage was 6 to 10 gr. the preparations have turned out to be not standardized in terms of US potency. If this was a *USP* preparation I should agree that untoward reactions at that level would be likely. My point was that, in contrast to the patient with myxedema and a basal metabolic rate of −40 per cent in whom even on 30 mg. of thyroid changes show clinically, this type of patient on up to 120 mg. is not affected at all.

DR. CASTLEMAN: Dr. Cobb, have you a comment?

DR. STANLEY COBB: I should like to emphasize that the patient had a psychosis for years that was considered to be a schizophrenic reaction. He was handled by Dr. White. I saw him from time to time as a consultant.

DR. THORN: We have seen patients with treated and untreated Addison's disease who had severe psychotic reactions; I am sure that a psychosis means more than adrenal insufficiency, but I am sure that the change in the adrenal hormone may be a factor in the development and manifestation of the psychosis.

DR. LE MOYNE WHITE: I followed this patient psychiatrically over the past eight years. Although I had the advantage at the outset of being aware of his organic defects, it is not in retrospect that I classify his mental difficulties as different from what we usually see in a patient with delusions and auditory hallucinations. I might almost say that his mental aberrations lacked the conviction and force that one would expect to see in the usual schizophrenic. There seemed to be very little progression, if any, in the hallucinations over the years, and this in itself is a distinguishing feature.

The patient was always relatively easy to handle, and although I could never change the "voices," he responded very well to reassurance. Without being able to go farther, I always believed that his physiologic depletion stood to his advantage in this respect.

I am certainly not impressed that cortisone made him worse. There was a great difficulty in ever knowing what he took. While he was in the hospital we could control his medication, but on the outside, he was very likely to throw away his thyroid tablets or, at the times when he felt depressed, to take a handful of cortisone.

DR. AUSTIN L. VICKERY: When you mentioned that this was a primary testicular atrophy, Dr. Thorn, did you mean to imply that it was unrelated to the other disease?

DR. THORN: I should say this was unrelated to the original disease. That diagnosis is based on the original biopsy and the presence of FSH. In a man of this age the only other conditions that would produce this picture and continue so long unchanged are amyloid disease or a queer monilia infection, of which he gave no evidence.

DR. WILLIAM H. BAKER: Do you think that this is consistent with so-called multiglandular fibrosis?

DR. THORN: I do not know what happens to the adrenal gland and thyroid gland with pituitary insufficiency for eighteen years. The interesting thing was the response to TSH that was demonstrated. If an ACTH test had been done it would be extremely interesting to me because it would tell a great deal about this man.

DR. CASTLEMAN: Dr. Henneman, you saw this patient.

DR. PHILIP H. HENNEMAN: Actually, Dr. Fuller Albright and Dr. Anne Forbes followed this patient for over ten years. It was their impression that he had panhypopituitarism. Since the presence of FSH in the urine of patients with panhypopituitarism is unusual the thought arose that this patient may have had a pituitary tumor producing gonadotropin but suppressing the function of the remainder of the pituitary gland. The testicular biopsy was considered consistent with the endocrine assay; the tubules were normal, as one would expect with normal FSH excretion, whereas the Leydig cells were atrophic and primitive. The latter observation was consistent with the low urinary output of 17-ketosteroids. The testicular biopsy was thus consistent with primary pituitary insufficiency rather than primary testicular failure.

DR. CASTLEMAN: I should like to have Dr. Hanelin show the x-ray films.

DR. JOSEPH HANELIN: Many films of the skull were taken over the years, but only one taken about two years before the patient died still remains. The sella turcica is definitely enlarged (Fig. 1). By accepted standard measurements the maximal dimension of the sella is about 12 mm. anteroposteriorly and of similar depth. This sella turcica in anteroposterior dimension is very close to 17 mm. and about 13 or 14 mm. in depth. Interestingly enough the walls of the sella are relatively thick so that if a tumor were present it would have to have been very slow growing.

DR. CASTLEMAN: Have you any further comment, Dr. Thorn?

DR. THORN: No; I think it is extremely interesting that the x-ray films showed no change over the entire period.

CLINICAL DIAGNOSIS

Panhypopituitarism.

Dr. George W. Thorn's Diagnoses

Primary panhypopituitarism, with adrenal insufficiency and thyroid insufficiency.
Primary testicular atrophy.
?Relative insulin deficiency.

Figure 1. *Lateral View of the Skull, Showing the Enlarged Sella Turcica with Relatively Thick Walls.*

Anatomical Diagnoses

?Addison's disease.
Absence of adrenal glands, ?cortical atrophy.
Atrophy of anterior pituitary and thyroid glands, testes and heart.

Pathological Discussion

Dr. Castleman: A post-mortem examination was not performed at the time of death. When Dr. Albright heard about the patient's death a few weeks later, knowing how important it was to learn what anatomic changes had been producing the disease, he obtained permission to have the body exhumed and post-mortem examination performed. The body had been embalmed well, and the tissues were adequately preserved.

The pituitary gland was studied by Dr. Agnes Burt Russfield, of our laboratory. She has, as some of you know, been correlating the changes in the pituitary gland in all types of endocrine diseases, hoping eventually to learn which cells secrete the various hormones. I am sorry she is not here today. Grossly, the sella turcica was symmetrically enlarged, corresponding to the appearance on the x-ray films (Fig. 2). It was empty except for a thin shell of gray fibrous tissue weighing 0.350 gm. and measuring 2 by 3 mm. that lined the cavity. The inner surface of this tissue was connected to the brain by an unusually long pituitary stalk. There was no evidence of any cyst or extraneous tissue that may have compressed the pituitary body or enlarged the sella. Thus, we found a pituitary body that was about half the size of a normal gland. Microscopically, the tissue was well preserved, and the cell types were readily identified in spite of the long interval post mortem. The sections showed a thin layer of anterior-lobe cells between two layers of loose fibrous tissue, probably the pituitary capsule, but no fibrosis between the cells. In some places the dominant cells were normal chromophobes and acidophils and, in other places, amphophils and hypertrophic amphophils. Dr. Russfield believes that the amphophilic cells are the ones that may secrete many of the hormones such as growth hormone, ACTH, TSH and gonadotropin. No definite basophils were observed.

The thyroid gland was not decreased in size; it weighed 22 gm., which is about normal. Microscopically, it looked very much like a Hashimoto struma, with many lymphocytes and follicles and the remnants of acini. The testis also was markedly atrophied. We were unable to find any Leydig cells at all; all

Figure 2.

we found were tubular cells. The heart weighed only 290 gm., and there was marked atrophy of the myocardial fibers microscopically. It looked like an infant's heart.

We were unable to find any adrenal tissue at all although we made quasi-serial sections through the entire adrenal regions on both sides. This was probably, therefore, a primary disease of the adrenal glands — a primary Addison disease, with complete atrophy; the atrophy of the heart would fit in with that premise. Further evidence that the adrenal atrophy was primary, and not secondary to the pituitary changes, may be the absence of fibrosis or inflammatory cells between the pituitary cells — findings that we see in the usual case of panhypopituitarism that is due to a primary destructive process. Also, the thyroid gland in primary panhypopituitarism contains a great deal of fibrosis, which was not present in the case under discussion.

Discussing this case, Dr. Russfield stated that she believes that the adrenal atrophy, clinical evidence of adrenal insufficiency early in the disease, attacks of hypoglycemia, presence of cortin and FSH in the urine and the thyroiditis found at autopsy are all consistent with a diagnosis of primary Addison disease. The pituitary gland in inadequately treated Addison's disease shows a very high count of amphophils and hypertrophic amphophils and may become large enough to expand the sella. Prolonged hormone medication, on the other hand, will reduce the amphophils, increase normal chromophils, produce nuclear pyknosis and decrease pituitary weight. It seems possible, though by no means certain, that this patient had primary Addison disease with an initial pituitary enlargement that was gradually suppressed during his eleven years of hormone therapy. We have had 2 other cases of primary Addison disease, 1 with tuberculosis and 1 with marked cortical atrophy in which the sella was large and the pituitary gland small, indicating perhaps the same sequence of events.

Would you comment on the possibility that this was a primary Addison disease, Dr. Thorn?

DR. THORN: If this patient's metabolic rate stayed at −40 per cent because of lack of growth factor and lack of thyroid, one might say that the course of the primary Addison disease would have been modified by that low metabolic picture. In general I should say there were two unusual complicating features; one was the length of the course, and the other the fact that he had cortisone therapy during the last four years. The cortisone therapy may have been the turning factor in uncovering or discovering adrenal tissue. We know that at the time that corticosteroids were measured there was little or none of that material in the urine. The basal level of corticosteroid excretion would not be helpful in a case like this. There is no arguing the fact that at this stage the patient had Addison's disease by virtue of the fact that there was no demonstrable adrenal tissue. Two to five days of modified ACTH therapy would have given this answer. An ACTH test on this man would only have indicated Addison's disease; it would have revealed nothing about pituitary insufficiency.

DR. HENNEMAN: He did not have excessive pigmentation.

DR. THORN: I do not think that would throw it one way or the other. Did you find any adrenal medullary tissue?

DR. CASTLEMAN: No.

DR. THORN: Why did that disappear? I can understand why the cortex went, but why did the medulla disappear?

DR. CASTLEMAN: I do not know. Two pathologists went over the material in situ when the prosector did not find any adrenal tissue. We made innumerable sections through the areas where the adrenal glands should have been.

DR. THORN: The most interesting point that you made is that none of the glands showed an inflammatory response or any other evidence of a disease that destroyed tissue. This is the purest example of atrophy that I have ever seen. One wonders what happens when growth hormone is absent. Is this the sort of atrophy that can take place in highly cellular tissue in the absence of growth hormone?

A PHYSICIAN: Could this sequence of events have resulted from the primary weight loss at the beginning?

DR. THORN: One cannot draw an analogy between Addison's disease with relatively normal other hormones and Addison's disease with hypopituitarism. This is confusing to me. I have not seen any patients over a long period who had complete absence of the adrenal cortex and at the same time had deficiency of growth hormone and thyroid. I can tell you what will happen if they do not have the adrenal glands alone for any length of time, but with this combination I have no experience. I should think that the patient would not have been so likely to get along well during this period. I think this process was progressive throughout his life. The fact that this man got along by increasing his diet and perhaps adding salt in the early days strongly suggests that there was a persistent small amount of aldosterone production. This is consistent with secondary adrenal insufficiency.

DR. JOSEPH C. AUB: What is the relation of the schizophrenia?

DR. THORN: We have seen several patients with Addison's disease who were seriously psychotic. There have been psychotic reactions before as well as after cortisone treatment. It is common enough in Cushing's disease. I think the hormone administration is a very disturbing environmental change for persons with a background of potential psychologic disturbance. What will happen with hormone therapy I do not think one can predict. This man might have become acutely psychotic, or he might have taken it better than most of us. The psychologic reaction to hormone therapy is very unpredictable.

A PHYSICIAN: Will you tell us about the pancreatic islands?

DR. CASTLEMAN: The pancreatic islands were normal as far as we could make out. The patient died with a subdural hematoma from a fall that he had in the mental institution.

A PHYSICIAN: Why did he not have diabetes insipidus with such marked atrophy of the pituitary gland?

DR. CASTLEMAN: The posterior lobe was all right.

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PERILS OF THE PATIO

SINCE the advent of spring, according to recent advices,[1] an increasing number of requests is being received by allergists for information about what can be done for relief or protection against allergic reactions after stings of the hymenoptera. Except for perhaps the past three or four years inquiries such as these were rare, and fortunately so, since except for a few isolated reports little was available in the way of concrete information on therapy.

The number of reactions from the sting of bees, hornets, wasps, yellow jackets and others of the same general class seems to be increasing at a disturbing rate; Mueller and Hill[2] called attention to this fact not so long ago in these pages. Well aware of the serious implications of the reactions, these investigators studied the problem and outlined a program of immunization.

Why are these reactions on the increase? This, of course, makes for speculation, but one cause seems to be the search by a growing population for *Lebensraum* in suburban or rural areas, along with the trend to more outdoor living and amateur gardening. Having spent a good deal of their lives on asphalt and concrete, they now invade the haunts of the hymenoptera and spend the cocktail hour on outdoor patios surrounded by flowering shrubs. Much like the American Indian, the insects may resent this intrusion into their natural habitat. Incidentally, they are attracted to beer and sweet drinks, and quite often tumble in. If then quaffed they may sting in protest, with devastating results. If one must have a nip out of doors, one should look before sipping and sip from a container through which one can look.

Recognition of the insects and knowledge of their habits is helpful. This is described in a number of books on the subject, which may be found in most libraries. An example is the dangerous yellow jacket, a single "queen" starting her nest in the spring on the ground, often in an abandoned mole or mouse hole. With the coming of August and September the colony has grown to hundreds or thousands of stinging workers. On a sunny day hustling members of the colony may be quite easily seen flying out or coming home and giving every appearance of being just as busy as a bee. The location should be carefully noted and scrupulously eschewed until the nest is disposed of.

Persons will get stung by one or another of the hymenoptera. Who among them should be protected by some form of prophylactic treatment? The incidence of systemic allergic reactions after stings is probably extremely low. However, these are the reactions that are potentially dangerous, and anyone who has had such a reaction should receive some form of prophylactic treatment. In addition, it may be advisable to protect, in the same manner, anyone who has had a very severe local reaction or a number of local reactions of increasing severity.

Since accurate identification of the various stinging

insects is often impossible, prophylactic treatment should be carried out with the use of a combined extract of bee, hornet, paper wasp and yellow jacket, all common to the New England scene. These extracts may be obtained from a number of commercial sources, a list of which may be found elsewhere.[2] As in the treatment for pollinosis, skin titration to determine the degree of skin sensitivity is done initially with an extremely dilute extract. When treatment is being started 0.10 cc. of a tenfold dilution of the lowest concentration giving a clear-cut skin reaction may be injected subcutaneously, to be followed by injections of increasing amounts every four or five days until a "substantial" dose is reached. This, naturally, will vary among patients, depending on their sensitivity, and should be tailored to the individual need. Present knowledge suggests that treatment be maintained for at least two years or even longer.

All patients requiring prophylactic treatment, as well as their families, should be informed of the importance of the immediate administration of epinephrine in 1:1000 dilution subcutaneously after a sting, and this should be given as soon as possible. Intravenous injections of antihistaminics such as diphenhydramine (Benadryl) and tripelennamine (Pyribenzamine) are likewise helpful.

Unfortunately, prophylactic treatment as just described will do nothing to reduce the pain of the sting, in itself well calculated to discourage one from treading on the "toes" of one's 6-footed neighbors. Some perhaps more fatalistic than most will choose to accept the risk.

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POLIOMYELITIS AND ANTIVIVISECTION

At the same time that banner headlines were appearing in the daily press announcing the acceptance of the vaccine for protection against poliomyelitis and plans were evolving for universal inoculation of the American public, an advertisement appeared in the back pages of some of the same newspapers. The Society for the Prevention of Cruelty to Animals had inserted its plea for funds to make vivisection unlawful in this state. To the intelligent citizen whose thought processes were active enough to compare the two pronouncements, an inconsistency must have been obvious. The public, today, is educated enough in medical science to recognize that most medical advances have been made at the expense of the animal kingdom, both dumb and otherwise. No one condones needless suffering even when it is associated with necessary animal or human experimentation. It is generally accepted that to alleviate human suffering is the prime goal of the medical profession.

One wonders how many of those who so lavishly support the obstructive program of the antivivisection lobby utterly refuse modern medical care, and how the others can accept it and remain logical and consistent. In view of the number of contributors to the antivivisection cause one might assume that less vaccine would be necessary than had been estimated for Massachusetts.

A letter published in one of the daily newspapers at that time suggested that the supporters of antivivisection be prohibited from obtaining for themselves or their families any of the vaccine. This goes too far — since two wrongs fail to produce a right. The number of those subscribing to this backward philosophy of antivivisection who now openly deny themselves, on conscientious grounds, hope of cure, increased longevity and the alleviation of suffering offered by medical science will determine whether this movement is sincere or hypocritical.

DR. ROBERT M. GREEN

Dr. Robert M. Green, whose obituary appears elsewhere in this issue of the *Journal*, not only linked the *Journal's* past with its present; he was undoubtedly the most scholarly editor that it had in either era. Almost on his graduation from medical school in 1906 he had joined the staff as assistant editor under Dr. George B. Shattuck, who had assumed the editorship in the year of Green's birth and was still to retain it for another six years. Dr. Shattuck's tenure of thirty-one years was a record for the publication.

Robert Green no doubt also established some sort of record of his own by beginning his association with the *Journal* at the age of twenty-five and becoming editor-in-chief at thirty-four. It must have been no slight task for a busy obstetrician and anatomist to edit and supervise the publication of an independent weekly periodical on a part-time or spare-time basis. He gave up his editorship when the *Journal* was purchased by the Massachusetts Medical Society in 1921, but was persuaded to return to the editorial board in 1931, in a position that he retained until his death.

Except for the interruption occasioned by the change of ownership Dr. Green's service to the *Journal* thus covered a span of forty-nine years, and his loyalty and interest, derived partly from the fact of his grandfather, John Ware, having been one of the three founders of the *Boston Medical and Surgical Journal* in 1828, was never in abeyance.

Dr. Green's death leaves two persons who helped bridge the gap between the *Journal's* two major periods of existence. They are Dr. George Gilbert Smith, who became assistant editor to Dr. Green in 1915 and continued as an associate to Dr. Walter P. Bowers and later Dr. Robert N. Nye until 1937, and Miss Clara D. Davies, who came to the *Journal* as general secretary and assistant to the editor in 1920, retiring as executive editor this spring.

DEAN OF GENERAL PRACTITIONERS

As a practical reminder of the fact that the parable of the Talents obtains at all times, Dr. W. N. Pickles, president of the British College of General Practitioners, addressed the South Middlesex Division of the British Medical Association in May on "Research in General Practice." It is a subject with which he has long been familiar.

Dr. Pickles, as reported in the *British Medical Journal* last month, developed his thesis around the careers of three of Britain's famous general practitioners. Edward Jenner, although by no means the first of an eminent line, was the earliest in point of time of Pickles's trio—"a man who unhurriedly followed up a country belief and patiently waited to confirm it."

The treatise on typhoid fever of William Budd, a boy of twelve when Jenner died in 1823, is characterized by Dr. Pickles as "one of the treasures of the epidemiologist, and his cold reasoning is a pattern for all those who essay to study the natural history of disease." Budd's early professional career was as a country doctor, and it is against such a background that his epidemiologic studies stand out, although it was after he had become a consulting physician in Bristol that his major contributions were made. As he himself wrote, "Having been born and brought up in the village, I was personally acquainted with every inhabitant of it, and being, as a medical practitioner, in almost exclusive possession of the field, nearly everyone who fell ill, not only in the village itself but over a large area around it, came immediately under my care."

Sir James Mackenzie was the third example cited, but it is in Budd that one sees the similarity to Pickles himself, who, practicing in a rural community, availed himself of the unique opportunities afforded by an intimate knowledge of his surroundings and his people to make his own significant contributions to the study of epidemic disease. This is a story that has already been told in these pages.[1,2]

It is pleasant to announce that Dr. Pickles's friends and colleagues in this area will this month have the opportunity of welcoming him again. Before returning to England after his attendance at the annual meeting of the British Medical Association in Toronto he has promised to visit Boston, where he will be the guest of the Massachusetts Chapter of the American Academy of General Practice and the *Journal*, at a subscription dinner to be tendered in his honor on July 20. Fellows of the Society who wish to attend, with their guests, may communicate with Dr. R. Adelaide Draper, 1107 Washington Street, Dorchester.

References

1. Pickles, W. N. Epidemiology in country practice. *New Eng. J. Med.* **239**:419-427, 1948.
2. *Idem*. Sylvest's disease (Bornholm disease). *New Eng. J. Med.* **250**: 1033-1036, 1954.

A case was reported to the Boston Society for Medical Improvement in April, 1854 (See American Journal of the Medical Sciences, *July, 1854*) *by Dr. A. A. Hayes, the celebrated chemist, in which ice-cream, flavored with butyric acid ether, caused excessive sickness in several persons . . .*
Boston M. & S. J., *July 12, 1855*

MASSACHUSETTS MEDICAL SOCIETY

ROBERT MONTRAVILLE GREEN, 1880-1955

Dr. Robert Montraville Green, a former editor of the *Journal*, died on May 29 at the age of seventy-four. He was born in Boston, attended the Boston

Latin School and Harvard College (graduating *summa cum laude* in English and Classics with the Class of 1902), and received his degree from Harvard Medical School in 1906.

After graduation Dr. Green continued his training on the South Surgical Service at the Massachusetts General Hospital. Subsequently, he served as intern at the Children's Hospital and at the Boston Lying-in Hospital. In 1930 he became surgeon-in-chief of gynecology and obstetrics at the Boston City Hospital, a position that he held until July, 1942.

Dr. Green was deeply interested in anatomy, which he taught at the Harvard Medical School for forty years. His demonstrations in this branch of science were remarkable for their clarity, method of presentation and beauty of diction. In 1931 he wrote the text to the *Warren Handbook of Anatomy*. He became an associate professor of applied anatomy, a position from which he retired as emeritus in 1947.

Early in his career he manifested great interest in the literary aspects of medicine, examples of his efforts being *Litora Aliena, Men, Manners and Medicine* and *Ferne Halves*. He was a master of Greek and Latin; he translated a number of classical Greek and Latin texts, among them *Galen's Hygiene (De Sanitate Tuenda)*, published in 1951, and *Galvani's Commentary on Electricity*, published in 1953 (his *Asclepiades* will be published this summer). In 1953 *Quintus Horatius Flaccus*, a volume containing many of the odes of Horace, rendered into English verse by Dr. Green and the late Dr. Fred B. Lund, appeared.

A few months before his death Dr. Green wrote to the *Alumni Bulletin of the Harvard Medical School* that "One of the most important and pleasurable events in the current year is the prospective publication of my latest and largest literary production, the preparation and composition of which have occupied my leisure for the past half-century, entitled 'The Round Table; An Arthurian Romance Epic.'"

In 1906 Dr. Green joined the Staff of the *Boston Medical and Surgical Journal*, now the *New England Journal of Medicine*. He began as assistant editor, first under Dr. George C. Shattuck and then under Dr. E. Wyllys Taylor. In 1915 he became editor-in-chief and continued in this position until 1921, when the *Journal* was taken over by the Massachusetts Medical Society and Dr. Walter P. Bowers was made managing editor.

Dr. Green was a member of the Signet Society and Phi Beta Kappa at Harvard and, in later years, of the Harvard Club, the Aesculapian Club, the Harvard Faculty Club, the Massachusetts Medical Benevolent Society, the Republican Institution in the Town of Boston, the Massachusetts Charitable Fire Society, the Sons of the American Revolution, the Society of Colonial Wars, the Classical Association of New England and the Lodge of St. Andrew.

He leaves his wife, Dorothy Bradford Green, five daughters and four sons.

G.G.S.

CORRESPONDENCE

PRESCRIPTION FOR PHYSICIANS

To the Editor: Since anthropology can be defined as the science of man and woman, their work and play, it should be an unusually fascinating hobby for physicians. Since the field is not concerned with individuals but with groups, races and people, their daily activities and recreations in all their many facets, any similarity to the practice of medicine is remote. True, anthropology is a biologic as well as a social science, but it has historical and many other divisions from which to choose a hobby.

Cultural or social anthropologists, often called ethnologists, describe, analyze and try to account for the wide variety of activities and social life of human beings. Family customs, home life, diet inclination and preferences, social contacts, clothing, religion, music, painting, amusements and all other forms of cultural behavior are included in their inquiry. An amateur ethnologist need be little more than a tourist, but how really interesting a trip becomes when the unusual mental attitude of inquiry is incorporated into sightseeing!

Archeology, or prehistory, is another amazing science, very demanding in technic for the professional but wonderful relaxation as a hobby when results of study are written up in a book or displayed for public inspection. There are many local museums with valuable exhibits. Once he is aware of the purpose of the display and understands why the anthropologist considers the items worth showing, the story of the discovery with related geographic and geologic elements may sooner or later create enough enthusiasm in the spectator to prompt him to do a little field work. Archeology then becomes a good excuse to get away from office and city to isolated sites where one can relax, dress comfortably and get dirty doing manual labor, if only as a "sidewalk superintendent" at a street excavation.

The study of fossil man or human evolution has caused many arguments, even law suits, ever since some newspaperman misquoted Darwin to the effect that man was descended from apes, something Darwin neither stated nor wrote. What are the facts? This study project alone will call attention to books about science and of adventure unsuspected. By means of such books one becomes an armchair anthropologist.

Many special studies can be done by individual men or women as well as small or large groups of either or mixed sexes. Using the nearest museum for guidance, anyone can be oriented in a project compatible with his inclination and ability.

Verily, there is no more thrilling study than that of man and woman through the ages. Few who have adopted some field of anthropology as a hobby ever relinquish it. There is something of interest for all in a field requiring no special equipment. Collections, whether of Egyptian jewelry, Hopi pottery or records of native Chinese music, entail more expense but are also of value and provide lasting entertainment. What more can a hobby offer? I have often wondered why more physicians do not develop some phase of anthropology as a hobby. It is a good prescription.

JOSEPH B. RODDIN, M.D.

Phoenix, Arizona

CORTICOSTEROID AND NITROGEN MUSTARD THERAPY

To the Editor: The author of the report entitled "The Palliation and Remission of Cancer with Combined Corticosteroid and Nitrogen Mustard Therapy," in the March 24 issue of the *Journal* was apparently unaware of the observations previously reported in "The Effects of ACTH, Cortisone and Nitrogen Mustard on Malignant Diseases," by L. K. Alpert, H. J. Zimmerman and E. H. Scherr, at the Second Clinical ACTH Conference (Blakiston Company, 1951, Vol. 2, pp. 235-250).

I should like to endorse fully the comments in the editorial entitled "Treatment of Advanced Cancer" in the March 24 issue of the *Journal* so far as the difficulties involved in the critical evaluation of cancer therapy are concerned.

LOUIS K. ALPERT, M.D.

Washington, D. C.

To the Editor: Thank you for the opportunity of acknowledging the letter of Dr. L. K. Alpert in which he calls attention to his excellent publication, "The Effects of ACTH, Cortisone and Nitrogen Mustard on Malignant Diseases," which was published in 1951.

As noted in my report in the *Journal* the concept of combined corticosteroid and nitrogen mustard therapy first oc-

curred to me and was clinically implemented in 1950, when a review of the literature revealed no similar publications. It is evident, however, that Dr. Alpert's work was in progress at that time and was published in the following year.

Apparently, a third group in Europe was pursuing similar lines of research in 1950, and also was unaware of efforts in the same direction in this country. In 1951 Fellinger et al. presented an article entitled "Combination Treatment with Nitrogen Mustard and ACTH in Neoplastic Diseases of the Lymphatic System," in the *Wiener klinische Wochenschrift* (63: 572 and 573) that consisted of a preliminary report of an unusual response in a patient with radiation-resistant lymphatic leukemia.

WILLIAM D. MCCARTHY, M.D.
Oakland, California

BOOK REVIEWS

Proceedings of the First International Congress on Medical Librarianship. Libri, Vol. 3. London, 20-25, July, 1953. Edited by F.N.L. Poynter. 4°, paper, 451 pp., with illustrations. Copenhagen: Ejnar Munksgaard, 1954. Danish kroner 50.—.

The first international congress on medical libraries and medical librarianship was held in London in 1953. Representatives of many countries were present, including officials from most of the English-speaking countries of the world. The papers contributed to this congress have now been published as a volume of *Libri* and medical librarians are greatly indebted to Jean Anker and Svend Dahl, our Scandinavian friends, and to the publisher, Ejnar Munksgaard of Copenhagen, for their co-operation in publishing a volume of 450 pages covering the entire transactions of the congress. The book is skillfully edited by F.N.L. Poynter.

As the papers will not appear elsewhere, this book becomes an important addition to the history of medicine, for the congress marked an epoch in the development of medical librarianship throughout the world. The contributions, as would be expected, cover a wide range of interest. Of first importance are those on the role of the medical librarian in the world today. Secondly there are symposia on the medical libraries of the world, education and training for medical librarianship, the centralization of medical-library resources, classification of material and finally a brief symposium on historical subjects. The standards of the papers are exceptionally high but particular attention should be called to the thoughtful report by W. B. McDaniel on "The Rôle of the Medical Librarian," a sharp-eyed account by W. R. Bett, entitled "The Librarian's Rôle in the Writing of Papers by Medical Men," a general historical study by Robert Herrlinger on "The Trew Library in Erlangen" and another by K. W. Humphreys on "The Medical Books of the Mediaeval Friars." Papers of a more official nature concerned "The Revision of the Barnard Classification" by Cyril C. Barnard, "Education for Medical Librarianship in the United States" by Estelle Brodman, and a paper on the same subject covering Great Britain by W. J. Bishop, and finally an account given, with a great deal of sadness, by Ernest Wickersheimer on "The Destruction by Fire of the Medical Section of the National and University Library of Strasburg," a tragic occurrence late in World War II. The volume is accompanied by a number of illustrations of English libraries, some of the principal speakers, books and bookplates from the Trew Library, the ruins of the Strasburg Library and an excellent portrait of Sir Cecil Wakeley, president of the congress. The volume is excellently produced by the publisher. All medical librarians throughout the world and many others will be grateful for the careful documentation of this volume so important in the development of their particular interest.

HENRY R. VIETS, M.D.

Recent Developments in Psychosomatic Medicine. Edited by Eric D. Wittkower, M.D. 8°, cloth, 495 pp. Philadelphia: J. B. Lippincott Company, 1954. $10.00.

Since the monumental work, *Mind-Body and Emotions*, written by Dr. Flanders Dunbar, there has been enormous stimulation of interest and activity in this field of medicine. This book, edited by Dr. Eric D. Wittkower and Dr. R. A. Cleghorn, professor of psychiatry and associate professor of psychiatry, respectively, at McGill University Faculty of Medicine, covers recent developments in this rapidly expanding area. Although the Greeks had the concept of mind and body, it has remained for modern physicians, particularly those who have been working in the last twenty-five years, to do the most brilliant and outstanding work, and part of this growth has come about by crossfertilization with psychoanalytic theory in particular and an admixture of the concepts of dynamic psychology in general.

This volume is really a symposium, but it is remarkably well organized as symposia go. The two parts, general and specific, report the findings of about 30 authors in nearly as many sections. Drs. Wittkower and Cleghorn have performed a great work in assembling and editing this varied material, of which some is conjectural and others have immediate practical value. Especially interesting are two splendid chapters, by Dr. Lawrence S. Kubie, on "The Problem of Specificity in the Psychomatic Process" and "The Central Representation of the Symbolic Process in Relation to Psychomatic Disorders." Excellent chapters are also contributed by Dr. Theodore Lidz on "The Thyroid" and "Psychological Aspects of Diabetes Mellitus." In fact the offering in this book is so wide that the specialist can pick and choose what interests him most. The volume closes with a remarkably lucid and stimulating chapter by Dr. Iago Galdston entitled "Psychosocial Medicine," which is pregnant with ideas and pulsating with thinking about medicine in a new key. Selected references concerning each topic follow the separate chapters, and a fine index winds up the volume in such a way that the reader can easily find what he is looking for without much loss of time. This is unquestionably the most valuable single volume on psychiatry and somatic medicine published in recent years and will prove interesting and informative reading for most physicians.

MERRILL MOORE, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Die Bestimmung der fruchtbaren und unfruchtbaren Tage der Frau mit Hilfe der Körpertemperatur. By Dr. Med. Gerd K. Doring, lecturer in gynecology, Universität Tübingen. With a foreword by Prof. Dr. W. Bickenbach, director, Universität Tübingen. 8°, paper, 19 pp., with illustrations. Stuttgart: Georg Thieme, 1954. DM 1.90. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

The author describes a method for the control of conception by determining the fertile and nonfertile days in women by the use of body temperature.

Gerichtliche Medizin. By Dr. Gerhard Hansen, chief physician, Institut für Gerichtliche Medizin der Humboldt-Universität, Berlin. 8°, cloth, 240 pp., with 125 illustrations, some in color. Leipzig: Georg Thieme, 1954. DM 19.50.

The author has written a compact book on medicolegal medicine. The text is in two parts: general and special. The former deals with autopsy, examination of the cadaver, time of death, vital reactions and sudden natural death; the latter considers the causes, means and manner of death, including gunshot, stabbing, electric burns, poisoning and shock, abortion, blood alcohol, child death, determination of paternity, including blood grouping, the law and the physician, investigation technics, sexual question, and forensic psychiatry. There are some references and a good index; the publishing is excellent, especially the illustrative work. The book should be in collections on the subject.

Principles and Practice of Antibiotic Therapy. By Henry Welch. Specially edited by Félix Martí-Ibáñez. 8°, cloth, 699 pp., with illustrations. New York: Medical Encyclopedia, Incorporated, 1954. (Distributed by Blakiston Company, Philadelphia.) $12.00.

This book, an expansion and enlargement of the previous volume of Welch and Lewis published in 1951 as *Antibiotic Therapy*, practically constitutes a new work. It was written by 17 specialists in their particular fields. The text is divided into three parts: the various antibiotics; the antibiotic treatment of infectious diseases, including virus and rickettsial diseases; and the treatment in the medical specialties, including ophthalmology, pediatrics and oral surgery and dentistry. Lists of references are appended to the chapters, and there is a good index. The book should be in all medical libraries.

Sterilisations-Methoden für die pharmazeutische und ärztliche Praxis. Erweiterung der im deutschen Arzneibuch aufgestellten Richtlinien über Sterilisation. By Prof. Dr. C. L. Lautenschläger, Frankfurt/M. Hoechst-Wuppertal-Elberfeld; and Prof. Dr. H. Schmidt, Marburg/L. 8°, cloth, 320 pp., with 67 illustrations. Stuttgart: Georg Thieme, 1954. DM 29.70.

The author has presented a comprehensive summary of sterilization and its methods for the physician and pharmacist. A valuable historical supplement gives the dates of events and discoveries in related subjects and divides them into various classes. There is a good index, and the book is well published. It is recommended for all medical-history collections.

The Graphomotor Projection Technique. Clinical Use and Standardization. By Samuel B. Kutash, Ph.D., chief, Clinical Psychology Section, Veterans Administration Hospital, East Orange, New Jersey, and lecturer in psychotherapy, Division of Graduate Studies, Brooklyn College; and Raymond H. Gehl, M.D., psychiatric consultant, Newark Regional Office, Mental Hygiene Clinic, Veterans Administration, and Montclair-Elizabeth Family and Children's Agencies, and practicing psychoanalyst, Newark, New Jersey. 8°, paper, 133 pp., with 55 illustrations and 17 tables. Springfield, Illinois: Charles C Thomas, 1954. $3.75. (Publication No. 218, *American Lecture Series.*)

The authors, in this monograph, describe the administration, scoring and interpretation of their method of personality study carried on during the past five years. There is a chapter on the clinical use of the technic and histories of 6 cases. There is a list of 42 references and a good index.

Anesthesia in General Practice. By Stuart C. Cullen, M.D., chairman, Division of Anesthesiology, Department of Surgery, State University of Iowa Hospitals, and professor of surgery (anesthesiology), State University of Iowa College of Medicine. Fourth edition. 12°, cloth, 312 pp., with 37 illustrations. Chicago: Year Book Publishers, Incorporated, 1954. $5.00.

This manual, first published in 1946, has gone through four editions and three reprintings, speaking well for its soundness and popularity. This new edition has been revised and brought up to date. There is a new chapter on ventilation and an extensive revision of the chapter on the muscle relaxants. There is a good index, and the publishing is excellent.

Physical Therapy after Amputation. The Treatment of the Unilateral Lower-Extremity Amputee. By Margaret Bryce. 12°, paper, 93 pp., with 14 illustrations. Madison: University of Wisconsin Press, 1954. $1.50.

The author describes physical therapy, in the clinic and at home, after amputation.

Clinical Approach to Jaundice. By Leon Schiff, M.D., Ph.D., professor of clinical medicine, Department of Internal Medicine, University of Cincinnati College of Medicine, and director, Gastric Laboratory, Cincinnati General Hospital. 8°, paper, 113 pp., with 52 illustrations. Springfield, Illinois: Charles C Thomas, 1954. $3.75. (Publication No. 202, *American Lecture Series.*)

The author discusses diagnosis and its importance in determining treatment in the various types of jaundice. The text is well illustrated; there is a short list of references and a good index.

The Concept of Schizophrenia. By W. F. McAuley, M.D., Belf., D.P.M., R.C.P.S.I., principal psychiatric registrar, Downshire Hospital, Northern Ireland. 8°, cloth, 145 pp. New York: Philosophical Library, 1954. $3.75.

This monograph discusses the present knowledge of schizophrenia and emphasizes the importance of heredity and environment in its genesis. The text proper is preceded by a short historical sketch. There is a bibliography and a good index.

The Bacterial Factor in Traumatic Shock. By Jacob Fine, M.D., Department of Surgery, Beth Israel Hospital and Harvard Medical School. 8°, paper, 82 pp., with 9 tables and 3 figures. Springfield, Illinois: Charles C Thomas, 1954. $2.75. (Publication No. 219, *American Lecture Series.*)

This monograph surveys the literature on the subject, and a list of 97 references is appended to the text. There is a good index.

Tuberculostatica und Moderne Tuberkulose-Behandlung. By Dr. Med. E. R. Mordasini. 8°, cloth, 307 pp., with 100 illustrations. Basel: Benno Schwabe and Company, 1954. Geb. Fr. 32.— (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

This is an important book on the treatment of tuberculosis by antibiotics and chemotherapy. The text is divided into two parts: general and special. The general part deals with the specific antibiotics (especially streptomycin), the chemotherapeutic agents and combination therapy. The special part discusses the treatment of tuberculosis of the systems and organs of the body. The literature is reviewed, and bibliographies are appended to the chapters. There is a good index and the book is recommended for all collections on tuberculosis.

Heart Disease and Industry: With particular reference to Workmen's Compensation cases. By Meyer Texon, M.D.; with forewords by Samuel A. Levine, M.D., and Hubert Winston Smith, LL.B., M.D. 4°, cloth, 324 pp. New York, New York: Grune and Stratton, 1954. $7.50.

The author has based his study on his experience with Workmen's Compensation cases and a complete analysis of 100 cases. Each case contains an abstract of its main features and its legal disposition. The text is divided into three divisions on the nature of the study, the 100 cases and coronary occlusion. There is a bibliography of 230 references and a good index. This is an important book, and it is recommended for all medical libraries and for all collections on the heart and occupational medicine.

Hand Atlas and Textbook of Human Anatomy. By Werner Spalteholz, late professor of anatomy, University of Leipzig. (Fifteenth atlas edition revised and enlarged by Rudolf Spanner, professor of anatomy, Cologne.) 2 v. 8°, Bd. Part 1, *Muscular System and Osteology.* 589 plates. Part 2, *Vascular System, Viscera, Nervous System, Sense Organs.* 774 plates. Amsterdam, Scheltema and Holkema (Boston: Little, Brown and Company), 1954. $11.50 per volume.

This edition of a standard atlas of anatomy has been revised and made available to American users by a Boston publishing house.

Thoraloskopische Eingriffe am Nervensystem. By Dr. med. E. Kux, lecturer, Surgical Clinic, Universität Innsbruck. 8°, Bd., 130 pp., with 48 illustrations partly polychromatic. Stuttgart, Georg Thieme, 1954. DM 28.50. (Distributed by Grune and Stratton, New York City.)

This special monograph surveys the modern literature of thoracoscopy of the nervous system. The text is divided into two parts. The first deals with methods and technic, including pneumothorax, risks and complications and a table of cases; the second discusses indications for the procedure, including ulcer of the intestinal tract, angina pectoris, hypertension, lung tuberculosis, diabetes mellitus and parenchymatous icterus. Lists of references are appended to the chapters. There is an extensive author index.

Atlas postomortaler Angiogramme. By Dr. J. Schoenmachers, professor of pathological anatomy; and D. H. Vieten, lecturer in medical roentgenology. F°, Bd., 203 pp., with 145 illustrations. Stuttgart, Georg Thieme. DM 57. (*Fortschritte a.d. Gebiete der Röntgenstrahlen, Ergänzungsband* 69; distributed by Intercontinental Medical Book Corporation, New York City.)

This semiatlas depicts post-mortem radiograms of the blood vessels of various parts of the body. The text is divided into two parts: general and special. The first describes the technic. The second presents pictures, with descriptive text, of the lung, brain, heart, kidney, trunk, fetus, portal system and veins. There is a comprehensive index, and the publishing is excellent.

Textbook of Pediatrics. Edited by Waldo E. Nelson, M.D., professor of pediatrics, Temple University School of Medicine, and medical director, Saint Christopher's Hospital for Children, Philadelphia. Sixth edition. 4°, cloth, 1581 pp., with 127 tables and 440 illustrations. Philadelphia: W. B. Saunders Company, 1954. $15.00.

The first edition of this comprehensive textbook was published in 1933. This new edition is the work of 72 contributors, and the material has been brought up to date. Short lists of references are appended to the subjects. There is a good index, and the book is well published. It should be in collections on pediatrics.

The Encyclopedia of Child Care and Guidance. Edited by Sidonie Matsner Gruenberg, special consultant, Child Study Association of America. 8°, cloth, 1016 pp., with illustrations. Garden City, New York: Doubleday and Company, Incorporated, 1954. $7.50.

This is a comprehensive reference book for parents. The first part of text (604 pages) consists of a large number of subjects, arranged alphabetically, on child care, guidance and diseases. The second part comprises 30 chapters on the basic aspects of child development.

Progress in Neurology and Psychiatry: An annual review. Vol. 9. Edited by E. A. Spiegel, M.D., professor of neurology and head, Department of Experimental Neurology, Temple University School of Medicine. 8°, cloth, 632 pp. New York: Grune and Stratton, 1954. $10.00.

This new volume of a standard series presents 35 review articles in the fields of the basic sciences, neurology and neurosurgery. Extensive lists of references are appended to the articles, and there is an index. The complete set is recommended for collections on neurology.

Neck Dissections. By James Barrett Brown, M.D., professor of clinical surgery, Washington University School of Medicine, and chief consultant in plastic surgery, United States Veterans Administration, Washington, D.C.; and Frank McDowell, M.D., assistant professor of clinical surgery, Washington University School of Medicine. 8°, cloth, 163 pp., with 82 illustrations. Springfield, Illinois: Charles C Thomas, 1954. (Publication No. 207, *American Lecture Series.*)

The authors discuss in detail, with illustrations, the procedure of neck dissections of cervical metastases from cancers of the mouth and lip. The literature is noted, and there is a bibliography of 267 items, as well as an extensive index.

Spirit and Nature; Papers from the Eranos Yearbooks. Translated by Ralph Manheim and R. F. C. Hull. (*Bollingen Series* XXX-1.) 8°, cloth, 492 pp. New York: Pantheon Books, Incorporated, 1954. $5.00.

This collected volume contains 13 papers by Jung, Dessauer, Kerényi and others. There is a listing of the contents of 22 volumes of the *Eranos–Jahrbücher* from 1933 through 1953. There is a good index, and the publishing is excellent.

Psychophysiologic Medicine. By Eugene Ziskind, M.D., clinical professor of psychiatry, University of Southern California School of Medicine, head, Department of Psychiatry and Neurology, Cedars of Lebanon Hospital, and senior attending psychiatrist, Los Angeles County General Hospital. With a foreword by John C. Whitehorn, M.D., Henry Phipps Professor of Psychiatry, Johns Hopkins University School of Medicine, and psychiatrist-in-chief, Johns Hopkins Hospital. 8°, cloth, 357 pp. Philadelphia: Lea and Febiger, 1954. $7.00.

The author discusses the recognition, diagnosis and treatment of psychologic factors in illness. The therapeutic interview is treated fully. The second part deals with technics for physicians. The last chapter considers the diseases commonly called psychosomatic, including asthma, peptic ulcer, essential hypertension and ulcerative colitis. The literature has been reviewed, and there is a bibliography of 15 pages, as well as indexes of names and subjects. The book should be in all collections on the subject.

Medical Uses of Cortisone: Including hydrocortisone and corticotropin. Edited by Francis D. W. Lukens, M.D., professor of medicine and director, George S. Cox Medical Research Institute, University of Pennsylvania School of Medicine. 8°, cloth, 534 pp., with 34 tables and 51 illustrations. New York: Blakiston Company, 1954. $7.50.

This collected work contains 29 articles on the use of cortisone in various diseases to which it is applicable. The preliminary chapters discuss the physiology of the adrenal cortex, the pharmacologic aspects of adrenocortical hormones in man and their effects in adrenal insufficiency. Lists of references are appended to the chapters, and there is an index. The book is recommended for all medical libraries.

Practical Obstetrics. By Bruce T. Mayes, M.V.O., M.B., B.S. (Sydney), F.R.C.S. (Edin.), F.R.A.C.S., F.R.C.O.G., professor of obstetrics, University of Sydney, and senior obstetrician, King George V Memorial Hospital for Mothers and Babies, Sydney, Australia. 8°, cloth, 500 pp., with 181 illustrations and 13 colored plates. London: Angus and Robertson, 1954. $12.19.

This book was first published in 1927 and reprinted in 1948. The new edition has been revised and enlarged. It is emphasized that it is not a textbook but a discussion of problems arising in the consultation room, at the bedside and in the ward and the operating room. This practical book is well illustrated and well published.

Hypoglycemia and the Hypoglycemic Syndrome. By A. J. Kauvar, M.D., assistant clinical professor of medicine, University of Colorado School of Medicine, and attending physician in gastroenterology, Colorado General Hospital and Denver General Hospital; and Martin G. Goldner, M.D., clinical associate professor of medicine, State University of New York Medical Center at New York, and director of medicine, Jewish Sanitarium and Hospital for Chronic Diseases, Brooklyn, New York. 8°, paper, 67 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1954. $3.00. (Publication No. 1955, *American Lecture Series.*)

The authors discuss the hypoglycemic syndrome and its differential diagnosis. The literature is reviewed, and there is a bibliography of 153 references.

NONCLINICAL NOTES

RUBIN AWARD

Dr. Joseph T. Velardo, research associate at the Peter Bent Brigham Hospital, has won the Rubin Award given by the American Society for the Study of Sterility. Dr. Velardo, at the eleventh annual meeting of the Society, presented a paper describing scientific evidence that hormonal imbalance of the lining of the uterus plays a decisive part in the failures of conception.

NOTICES

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

Applications for certification for the Part I Examinations of the American Board of Obstetrics and Gynecology are now being accepted. Candidates are urged to make application as early as possible and before October 1, 1955.

AMERICAN DERMATOLOGICAL ASSOCIATION PRIZE-ESSAY CONTEST

The American Dermatological Association announces the annual award of $1400 (first prize $500, second prize $400, third prize $300 and fourth prize $200) for essays relative to some fundamental aspect of dermatology or syphilology.

Competition is open to scientists generally, not necessarily to physicians.

The essay awarded first prize may be presented before the annual meeting of the American Dermatological Association with expenses paid in addition to the $500 prize.

Essays must be received by the secretary not later than November 15, 1955. Further information may be obtained from the secretary, Dr. J. Lamar Callaway, American Dermatological Association, Duke Hospital, North Carolina.

SOCIETY MEETINGS AND CONFERENCES

July, August and September. Beth Israel Hospital Course. Page 509, issue of March 24.

July 11–August 23. Consultation Clinics for Crippled Children in Massachusetts. Page 1099, issue of June 23.

July 14 and 15. Symposium on Tuberculosis. Page 509, issue of March 24.

July 14–16. Congress of Nobel Prize Winners. Page 510, issue of March 24.

August 28–September 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.

August 30 and 31 and September 1. New England Health Institute. Page 1010, issue of June 9.

October 6–8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.

October 22–26. American Heart Association. Scientific Session. Page 603, issue of April 7.

October 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.

November 1–3. Henry Ford Hospital Symposium on Enzymes. Page 920, issue of May 26.

November 6–13. Second International Congress of Allergology. Page 157, issue of January 27.

November 11 and 12. Inter-Society Council. Page 1056, issue of June 16.

November 14 and 25. Course in Laboratory Diagnosis of Tuberculosis. Page 1102, issue of June 23.

November 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.

November 29–December 2. Interim Session of the American Medical Association, Boston.

Thursday, July 14

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:00 m. Thoracic Conference. Unusual Medical and Surgical Thoracic Problems from "The Circuit." Drs. Hugh E. Wilson and Warren J. Taylor. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

Friday, July 15

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

Saturday, July 16

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

Monday, July 18

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon and staff. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Dr. Vandam. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. MacMahon and Staff. Stearns Auditorium, New England Center Hospital.

Tuesday, July 19

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic (Cafeteria), New England Deaconess Hospital.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

Wednesday, July 20

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.